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HEART FAILURE OR ACUTE NEPHRITIS WITH ONSET ABOUT THREE WEEKS AFTER DELIVERY *

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THE vast literature of the abnormal puerperium concerns itself almost entirely with complications immediately preceding labor, during labor, and in the first ten days postpartum. Those complications manifested later, especially with an interval of apparent health before their development, have received but little consideration. A group of cases representing such puerperal complications has been seen in the Tulane medical unit of the Charity Hospital of Louisiana. At least two distinct groups have been recognized, (1) patients without evidence of disease until the puerperal period, who, within three to five days following delivery, developed signs of sepsis, followed in 14 to 21 days by the appearance of acute, diffuse hemorrhagic nephritis, and (2) those patients who, 14 to 25 days postpartal, developed frank congestive heart failure in spite of the fact that during pregnancy and labor there had been no definite evidence of heart disease. Search of the obstetrical and medical literature reveals that these clinical pictures are not well known, and that they have been inadequately and unsystematically described. This paper is an attempt not only to establish a tentative classification of these syndromes but also to discuss the probable mechanisms of symptom production as they are peculiarly related to the puerperal state, and to emphasize the relationship between pregnancy and these symptoms.

These types are illustrated by the following case reports:

CASE REPORTS

Case 1. J. D., married negress, aged 38, entered the Charity Hospital October 1, 1933, complaining of edema of the face and lower extremities. Her health in the past had been generally good. There was no history of soreness of the throat nor of scarlet fever. She had been pregnant six times. All pregnancies went to full term except the fifth which resulted in miscarriage at four months. She applied

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to the obstetrical out-patient department in the early months of the last pregnancy. No signs of toxemia were ever noted. On August 7, 1933, she complained of constipation and slight swelling of the feet. Blood pressure was then 106 mm. of mercury systolic and 70 diastolic. Urinalysis showed no albumin, sugar, casts nor red blood cells. On September 2, 1933, the urinalysis was again unchanged. She came to the hospital in labor on September 6, 1933, and delivered spontaneously a full term child. No untoward symptoms developed until the second day postpartum when she experienced chills and fever, symptoms which remained for five days in varying degree, the temperature reaching 103° F. The lochia appeared normal. The temperature then returned to normal and the patient was discharged on the fourteenth day. Urinalysis had disclosed no cause for the fever. The patient then led a restricted life with freedom from symptoms until the tenth day at home when she awakened in the morning and noted a puffiness about the eyes and edema of the feet and hands. Severe frontal headaches developed. The urine became red and reduced in amount for three days. Palpitation for three to four minute intervals was noted at times and dyspnea occurred on exertion. A dry cough ensued. There were no dizziness, spots before the eyes, nor sore throat. Because the symptoms failed to subside she applied for admission to the hospital.

Examination on admission disclosed a well developed and well nourished negress of sthenic habitus, lying quietly in bed. The height was 65 inches; weight 120 pounds; blood pressure 160 systolic and 90 diastolic; respiration 20 per minute; pulse 86 per minute; temperature 98.6° F. She did not appear acutely ill. A distinct puffiness was noted about the eyes. The pupils reacted to light and accommodation. The conjunctivae were pale. Oral hygiene was good. There were many gold fillings. The chest was symmetrical. The lungs were clear to physical examination. The heart was not demonstrably enlarged; P.M.I. was in the fifth interspace 7½ cm. from the midsternal line. The left border of cardiac dullness was 0.5 cm. further to the left. P_2 was less than A_2. There were no murmurs. The breasts were lactating. The abdomen showed slight diastasis recti. The lower border of the liver was barely palpable. Some deep tenderness below the right costal margin was elicited. No rigidity or muscle spasm was found. Pelvic examination disclosed a foul purulent discharge. The cervix was bilaterally lacerated. The fundus was felt anteriorly and showed subinvolution. No adnexal masses were felt. The extremities displayed a tense glistening skin with pitting edema below the knees. Venous pressure was not demonstrably elevated with hand placed upon the thigh.

Laboratory Work. On admission the blood findings were: red blood cells 3,270,000, white blood cells 9,500, hemoglobin 75 per cent, non-protein nitrogen 29, urea nitrogen 15, sugar 102 mg. per cent, Wassermann negative. The urine showed: specific gravity 1.012 to 1.014, albumin 14 per cent (wet), sugar negative, many hyaline, fine and coarse granular casts, six to eight red blood cells per high power field, numerous white blood cells per high power field. The phenolsulphonephthalein output was 30 per cent in two hours. The serum proteins on September 11, 1933, were: albumin 2.43, globulin 1.94, total 4.37 gm. per cent. Cystoscopic examination disclosed findings similar to those recorded above with no growth in cultures. Cervical cultures were negative for streptococci.

On discharge from the hospital on October 21, 1933, the urine still showed red blood cells, casts and albumin (7.8 per cent). The edema had entirely cleared and symptomatically the patient was relieved. The blood pressure was then 155 systolic and 90 diastolic. The patient returned home to an outlying parish to continue treatment with her local physician.

Case 2. A. M., married negress, aged 20, entered the hospital on March 22, 1933. She had not menstruated since January 1933, and complained of nausea and vomiting which were easily controlled. Physical examination at that time was not remarkable except for a three months pregnancy. There were no previous preg-

nancies. Laboratory data at that time disclosed the following: Urine showed a specific gravity of 1.024, albumin plus, sugar negative, no casts, no red blood cells, 10 white blood cells per high power field. The phenolsulphonephthalein output was 80 per cent in two hours; non-protein nitrogen 26 to 28, blood sugar 95 mg. per cent; red blood cells 4,395,000, white blood cells 6,000, hemoglobin 80 per cent.

She was not seen again until September 7, 1933, when she entered the hospital complaining of cramp-like abdominal pains and vaginal bleeding. The uterus was enlarged above the umbilicus and was contracting at intervals. On September 8, 1933, she aborted. There was little postpartal bleeding. The urine was negative for albumin, casts and red blood cells. The blood pressure was 130 systolic and 80 diastolic. The temperature, which was 103° F. on admission, dropped to normal on the third day. On the tenth day she was discharged.

She again applied for admission on November 28, 1933, complaining of dyspnea and pain in the right side of the chest. She stated that two weeks following her miscarriage she developed edema of the ankles. Her face appeared somewhat swollen. Urine became reduced in amount but was not discolored. There was no dyspnea, dizziness, nor spots before the eyes. Ankle edema continued, improving at times, but gradually becoming more severe and, for two weeks before admission, was accompanied by progressive dyspnea. There was no past history of sore throats nor scarlet fever.

Examination on admission disclosed a young negress lying propped up on the bed appearing seriously ill and obviously anemic. The face was edematous. Pupils reacted to light and accommodation. No exudate was seen in the fundi. Oral hygiene was good. The tonsils were not inflamed. The thyroid was bilaterally symmetrically enlarged. The lungs showed no evidence of congestion. The heart was enlarged to the left, the apex beat being one centimeter to the left of the midclavicular line in the fifth interspace. The rate was 100 per minute. The rhythm was regular. No murmurs were heard but a protodiastolic gallop rhythm was heard at the apex. The blood pressure was 144 systolic and 116 diastolic. The abdomen showed a fluid wave and shifting dullness. The liver was not felt. The legs and thighs showed marked pitting edema. Pelvic examination disclosed a bilaterally lacerated cervix.

Laboratory Work. The urine was acid, specific gravity 1.016, albumin +++, occasional white blood cells, 10 to 15 red blood cells per high power field, many coarse and fine granular casts. An Addis count on January 6, 1934, disclosed casts 684,000, red blood cells 24,320,000, epithelial and white blood cells 56,130,000. An examination of the blood showed 2,700,000 red blood cells, 9,400 white blood cells, hemoglobin 50 per cent. The phenolsulphonephthalein was 40 per cent in two hours. The non-protein nitrogen was 28, urea nitrogen 13, creatinine 1.0, sugar 83 mg. per cent. The Wassermann was strongly positive. The serum proteins were: albumin 1.90, globulin 2.59, total 4.49 gm. per cent. The electrocardiogram showed T_1 inverted and a sinus tachycardia. The teleoroentgenogram showed the transverse diameter of the chest to be 27 cm., the transverse diameter of the heart 17.3 cm. The basal metabolic rate was + 2 per cent.

The patient improved symptomatically and, on December 23, 1933, signed her own discharge. On January 1, 1934, eight days later, she was readmitted with edema more marked than before. Besides the marked generalized edema and ascites, there was a bilateral hydrothorax. The blood pressure was 165 systolic and 120 diastolic. Small areas of exudation were seen in the macular region on fundus examination. The non-protein nitrogen rose to 52 mg. per cent, urea nitrogen to 27. The urine was essentially unchanged. The phenolsulphonephthalein was 15 per cent in two hours. The patient went into coma and died in two days. No autopsy was obtained.

Case 3. P. W., negress, aged 22, entered the Charity Hospital on October 5, 1933, complaining of headache and swelling of the face and ankles. In the past she

had been well. She had had a sore throat in 1930. There was no history of scarlet fever nor of joint pains. She became pregnant for the first time in January 1933, and attended the obstetrical clinic for antepartum care. No significant symptoms arose during this period. Blood pressure varied from 120 systolic and 82 diastolic to 118 systolic and 78 diastolic. The urine was repeatedly negative for albumin, sugar, red blood cells and casts. No edema nor headache developed. On September 10, 1937, she delivered spontaneously a 7½ pound child which lived 15 days. Blood pressure during labor rose to 144 systolic and 88 diastolic. On the third day postpartum she began to have fever which lasted three days and reached 103° F. A chill accompanied the onset of fever. The urine appeared dark brown for several days following the chills and fever, and burned on passage. Pus cells only were found at this time. She was discharged on September 21, 1933. Several days later she noticed for the first time swelling of her face, especially about the eyes, and also of the legs. Severe frontal and parietal headache developed with slight vertigo and spots before the eyes. She became nauseated but did not vomit. Symptoms became progressively worse. Headache became so severe that she walked the floor at night and cried out in pain. Her neck felt stiff.

Examination on admission disclosed an hypersthenic young negress lying very restlessly in bed, holding her head in her hands and obviously in great pain. The facies was anxious. The height was 65 inches, weight 130 pounds, blood pressure 175 systolic and 125 diastolic, respiration 22 per minute, pulse 100 per minute, temperature 99° F. The face was markedly edematous, the eyes almost closed with the edema. Pupils reacted to light and accommodation. Mucous membranes were pale. The tonsils were not inflamed. The breasts were lactating. The lungs were not remarkable. Heart: Point of maximum impulse was found 10 cm. from the midsternal line in the fifth interspace, the left border of cardiac dullness 10.5 cm. from the midsternal line in the fifth interspace. A harsh blowing systolic murmur was heard along the left border of the sternum. P_2 was greater than A_2, and both were accentuated. In the abdomen no signs of fluid were elicited. The liver and spleen were not felt. Pelvic examination disclosed subinvolution and retrodisplacement of the uterus. The cervix was soft. The extremities displayed moderate pitting edema in the lower half of both legs.

Laboratory Work. On admission the urine was acid, the specific gravity 1.018, albumin ++, sugar negative. A few red blood cells and fine granular casts were found. An Addis count on October 28, 1933, disclosed a volume of 300 c.c., red blood cells 156,000,000, casts 750,000, pus and epithelial cells 75,000,000. Nonprotein nitrogen was 28, blood sugar 88 mg. per cent. Blood Wassermann was negative. Serum proteins on October 8, 1933, were: albumin 3.13, globulin 2.34, total 5.47 gm. per cent. The teleoroentgenogram showed the transverse diameter of the chest to be 25 cm., transverse diameter of the heart 13.5. Spinal fluid examination showed a pressure of 10 mm. of mercury, less than 10 cells per cubic millimeter, Wassermann negative, no red blood cells and a negative globulin reaction.

The edema rapidly disappeared with treatment. The urinary protein diminished markedly and the hematuria became very slight. Blood pressure fell only to 170 systolic and 115 diastolic. On November 2, 1933, the patient was discharged to her local physician for treatment at home.

Case 4. V. S., 16 year old negress, gave a history similar to that of Case 3 except for a forceps delivery. On the nineteenth day postpartum she suddenly developed headache and dizziness. Edema of the eyes and ankles developed on the twenty-fourth day postpartum and lasted one day only. The next day headache became more severe, blurring of vision ensued, and she suddenly had a generalized convulsion, which prompted admission on November 11, 1933. She had had occasional sore throats when a child.

Examination disclosed evidence of the convulsion in a beefy, bleeding tongue.

There was moderate edema of the face and legs. The ocular fundi were negative except for narrowed arteries. The breasts were lactating. The heart and lungs were not remarkable. The blood pressure was 158 systolic and 104 diastolic. Pelvic examination disclosed a subinvoluted uterus.

Laboratory Work. Spinal fluid pressure was 14 mm. of mercury, cells less than 10, globulin, Wassermann and gum mastic negative. Blood chemistry disclosed non-protein nitrogen 27, blood sugar 70 mg. per cent. Urine showed a specific gravity of 1.020, acid, albumin +++, many red blood cells and coarse granular casts on three examinations (catheterized). Phenolsulphonephthalein was 45 per cent in two hours.

She had two convulsions after admission and then symptoms receded. By November 15, 1933, date of discharge, she was symptom free. The edema and urinary findings had disappeared and the blood pressure was 140 systolic and 70 diastolic.

Case 5. D. H., 25 year old negress, entered the Charity Hospital on October 9, 1933, and delivered a full term child the next day by forceps delivery. There was no evidence of renal disease at that time. The blood pressure was not elevated. The postpartal stay in the hospital was uneventful except for a rise of temperature to 101° F. on the fourth and fifth days. About 16 days postpartum she experienced a severe headache, and her vision blurred at times. She felt feverish but did not take her temperature. Edema made its appearance about the face and ankles. Symptoms continued and on November 9, 1933, 29 days after delivery, generalized twitching movements unaccompanied by loss of consciousness prompted admission to the hospital. In the past there was no history of rheumatic fever, scarlet fever, nor acute tonsillitis. She had been pregnant five times before, resulting in four miscarriages and one full term living child.

Examination disclosed generalized edema, especially noticeable over the eyelids. The blood pressure was 156 systolic and 100 diastolic, temperature 98° F., pulse 90 per minute. The retinal vessels appeared normal. The tonsils were enlarged but not acutely inflamed. The lungs showed some fine basal râles posteriorly. The heart was not demonstrably enlarged to the left. An apical systolic murmur, untransmitted, was heard. P_2 was greater than A_2. The abdomen showed no evidence of ascites. Pelvic examination was not done.

Laboratory Work. Examination of the urine showed a specific gravity of 1.016, cloudy, acid, albumin ++++, many red blood cells, white blood cells and coarse granular casts. The non-protein nitrogen was 30, blood sugar 97 mg. per cent and the Wassermann test weakly positive.

The patient became progressively worse. Dyspnea became more marked, basal râles increased until there was marked pulmonary edema. The blood pressure remained in the range of 168 systolic, 115 diastolic to 152 systolic and 92 diastolic. The pulse became thready and the patient died in acute heart failure. No autopsy could be obtained.

Case 6. A. T., married negress, aged 20, entered the Charity Hospital on February 27, 1934, complaining of swelling of the legs. In the past she had always been well. She had measles and mumps as a child but no sore throats, scarlet fever nor anything which might be construed as a streptococcal infection. There was no history of hematuria nor other urinary symptoms. The family history was irrelevant. She had had her first child two years before. At that time there was no edema, no urinary nor cardiac symptoms. Delivery was uneventful. She was well, then, until January 5, 1934, when she entered the obstetrical ward of Charity Hospital. For several days she had noted a slight swelling of the ankles which disappeared on lying down. The history at that time revealed no headache, vertigo, epistaxis, nausea nor urinary symptoms. There were no symptoms nor signs of eclampsia. Blood pressure was 122 systolic and 80 diastolic. Urine on three occasions showed no albumin, casts, nor red blood cells. On January 12, 1934, she delivered spontaneously. On

the first day postpartum the temperature rose suddenly to 101° F. and remained irregularly elevated until January 19, 1934, when it returned to and remained normal following the use of urinary antiseptics given because of the presence of white blood cells in the urine. She was discharged on January 21, 1934, and felt perfectly well for 14 days, when her ankles began to swell. No dyspnea nor vertigo developed. The urine became reduced in amount but no hematuria was noted. The edema became more marked so that on February 27, 1934, she again applied for admission.

Physical examination on admission disclosed a young, well nourished negress lying comfortably in bed. Oral temperature was 98.2° F., pulse 90 per minute, respiration 18 per minute, blood pressure 178 systolic and 100 diastolic (right), 180 systolic and 100 diastolic (left). There was no apparent puffiness of the face. Pupils were equal and regular and reacted to light and accommodation. The ocular fundi revealed no remarkable changes. Oral hygiene was good. The tonsils were enlarged but not reddened. The breasts were lactating, the lungs clear. The heart was not demonstrably enlarged. The sounds were clear. A_2 was greater than P_2. Sinus arrhythmia was present. No murmurs were heard. The abdomen revealed only a small umbilical hernia. Vaginal examination disclosed the fundus anterior, and the cervix bilaterally lacerated. No tenderness and no adnexal masses were palpated. The lower extremities revealed pitting edema extending up to the knees.

Laboratory Work. Urinalysis disclosed a specific gravity of 1.032, albumin ++++ (10 per cent wet), numerous casts and red blood cells, many white blood cells (catheterized). The phenolsulphonephthalein was 30 per cent in two hours. On March 5, 1934, an Addis count (catheterized) showed casts 38,500, red blood cells 770,000, white blood cells 1,925,000. Non-protein nitrogen was 28, blood sugar 92 mg. per cent; hemoglobin 80 per cent, and red blood cells 4,100,000. The Wassermann test was negative. Feces were negative for ova and parasites. The electrocardiogram showed no evidence of myocardial disease. Roentgen-ray of the chest disclosed clear lung fields, a transverse diameter of the chest of 27.2 cm., a transverse diameter of the heart of 13.5 cm. Cystoscopic examination (March 12, 1934) of the right kidney disclosed 10 to 20 red blood cells per high power field, 10 to 20 white blood cells per high power field; of the left kidney, 20 to 30 red blood cells per high power field, no growth on culture.

The albumin and red blood cells gradually diminished in amount until, on March 17, 1934, none were found in the urine. Small numbers of white blood cells remained. With the changes in urinary findings the edema disappeared and the blood pressure gradually dropped to 120 systolic and 80 diastolic. On March 17, 1934, the patient was discharged to her physician in an outlying parish.

*Case 7.** M. T., a colored primipara, aged 26 years, had been followed in a prenatal clinic and found to have a normal physical examination, blood pressure and urinalysis. Subsequent term delivery was uneventful and without instrumentation. Four days postpartum the temperature rose to 101° F. and returned to normal four days later. No localizing signs of infection were found. Lochia were normal. She was discharged to her home on the eighth day and 14 days later, 22 days following delivery and 18 days after the febrile puerperal episode, edema suddenly appeared in the face, feet and legs. Two days later the abdomen became distended. The urine was scanty and grossly red. Physical examination revealed a typically distributed nephritic edema, a blood pressure of 168 systolic and 102 diastolic, normal appearing tonsils, lactating breasts and negative lung findings. The heart was not demonstrably enlarged. Rhythm was regular; P_2 was greater than A_2. There were no murmurs. Venous pressure was normal. Ascites was present. Urinalysis showed 26 per cent albumin (moist), many fine granular casts and numerous red blood cells. Cervical culture disclosed hemolytic streptococcus and staphylococcus. The Wassermann was negative. Following a stormy course with hypertensive encephalopathic

* This case has been reported previously in Trans. Assoc. Am. Physicians, 1937, lii, 198.

attacks, the symptoms, signs and urinary findings cleared and the patient was discharged.

Case 8. O. H., married negress, aged 34, entered the hospital on December 2, 1933, complaining of shortness of breath. Her health in the past had been generally good. There was no history of sore throats, scarlet fever, cyanosis, dyspnea nor edema, except as stated below. There had been 11 pregnancies with all of which slight ankle edema was noted. Never had there been any symptoms of toxemia of pregnancy. Hypertension had never been noted and, when in this hospital with a pregnancy in June 1928, the laboratory findings, physical examination and blood pressure were normal. A pregnancy terminating in the delivery of normal twins on October 2, 1933, was accompanied by no symptoms except the usual slight ankle edema. However, several days following the delivery the patient became suddenly short of breath and was relieved only by sitting up. Palpitation accompanied the attack of dyspnea. Similar attacks occurred several times daily, lasted 15 to 30 minutes, and were relieved only by assuming the sitting position. During these attacks a severe feeling of oppression was felt substernally and a dry hacking cough developed. The edema of the ankles, which in previous pregnancies had quickly subsided on bed rest, not only remained but extended from the ankles to the thighs and abdomen. Dyspnea, at first paroxysmal, became evident at all times. Rest in bed and medication at home were of no avail so the patient applied for admission to the hospital.

Physical examination on admission disclosed a 35 year old negress lying propped up in bed and breathing with difficulty. The pupils reacted to light and accommodation. The retinal vessels showed moderate sclerosis only. The thyroid gland was not palpable. The mouth showed poor oral hygiene with many carious teeth and a foul breath. On examination of the lungs the breathing was found to be symmetrical but labored. Coarse râles were heard in both bases. The bases failed to descend with respiration and impairment of resonance, with diminished breath and voice sounds, was noted. The heart was demonstrably enlarged. The left border of cardiac dullness was percussed 16 cm. to the left of the midsternal line in the fifth left interspace. M_1 was muffled. There was a blowing localized systolic mitral murmur which did not replace the first sound. P_2 was greater than A_2 and loud and tambour-like. Occasional extrasystoles were heard. Blood pressure was 138 systolic and 116 diastolic. The abdomen was distended. A fluid wave and shifting dullness were elicited. The liver edge was felt 5 cm. below the costal margin. External genitals were negative. The perineum was relaxed. Pelvic examination disclosed a congested cervix which was enlarged and bilaterally lacerated. A mucopurulent discharge was present. There were no adnexal masses nor tenderness. Moderate arteriosclerosis was present in the extremities. There was pitting edema of the lower extremities to the thighs. Sacral edema was also present.

Laboratory Work. Urine (voided) showed only a trace of albumin. Addis count (catheterized) showed no casts, pus cells 2,252,000, red blood cells 247,580. Phenolsulphonephthalein was 25 per cent in two hours. Examination of the blood showed hemoglobin 70 per cent, red blood cells 3,250,000, white blood cells 5,250. The differential formula was normal. Non-protein nitrogen was 28, creatinine 1.2, blood sugar 100 mg. per cent. Wassermann and feces were negative. The electrocardiogram showed low voltage QRS in all leads, prominent and notched P_2, inverted T_1 and T_2. Roentgenogram of the chest disclosed evidence of fluid in both pleural cavities. This made cardiac measurements inaccurate but the heart appeared definitely enlarged.

The patient reacted well to treatment directed toward congestive heart failure and, by December 8, 1933, became symptom free and free from edema. On December 16, 1933, she was discharged to the Out-Patient Department for treatment.

Case 9. J. R., aged 25, married negress, entered the hospital on February 7,

1934, complaining of shortness of breath. Her health in the past had been generally good. There was no history of sore throats, scarlet fever, syphilis nor manifestations of the rheumatic syndrome. On March 6, 1927, she was confined at another hospital. All findings, including the Wassermann, were then negative. Four years previously she complained of pain in her legs which later became swollen. Both knees and ankles felt stiff and she was unable to walk because of the pain. There was no fever nor other symptoms which could be elicited. A doctor advised elastic stockings which she wore for several weeks, after which she felt perfectly well.

On December 3, 1933, the patient gave birth to a normal seven pound child. The delivery by a midwife was accompanied by no dystocia, and no instruments were used. This, as three previous pregnancies, was accompanied by no untoward symptoms whatsoever. No edema nor dyspnea was ever noted. The lying-in period was uneventful. No fever nor chills were noted and the patient got up on the seventh day and began to do her housework. The lochia were normal, as she described them.

Twenty-one days following delivery she was seized with violent colicky pains around the umbilicus, so severe that she had to lie down, double up, and scream with pain. There was no radiation. The pains lasted about an hour and gradually disappeared. She went to sleep to be awakened several hours later with marked dyspnea relieved only by sitting up in bed. There was no associated pain. The attack lasted about half an hour, when she was again able to lie down and sleep. No shortness of breath on exertion was noted on the next day, but two days later she noted some dyspnea on doing her usual housework. The paroxysmal dyspnea recurred nightly and within 10 days dyspnea was present when at rest during the day and she could no longer lie down. The ankles and abdomen began to swell. On February 3, 1934, she began to notice a brownish foul vaginal discharge. Edema became very severe and she was admitted to Charity Hospital on February 7, 1934.

Physical examination on admission revealed a young negress lying propped up in bed breathing rapidly and shallowly, and apparently gravely ill. The skin was cold and clammy. The pulse was rapid and thready and the blood pressure could not be obtained. Hurried examination revealed pulmonary edema, enlargement of the liver and dependent edema. Treatment was instituted with intravenous digitalis, morphine, heat, and 50 per cent glucose. In two hours the pulse was 103, temperature 99.8° F., and blood pressure 145 systolic and 100 diastolic. Four hours later the pulse was 102 and of good volume. Dyspnea was less marked.

More complete physical examination the next day revealed the following pertinent points: temperature 101° F., pulse 56 per minute, respiration 20 per minute. The left pupil was irregular. The tonsils were not inflamed. Breasts were lactating. Lungs showed moisture at both bases. In examining the heart the apex beat was neither seen nor felt. The left border of cardiac dullness was found 7.5 cm. from the midsternal line in the fifth left interspace. P_2 was greater than A_2. A soft systolic murmur was heard in the tricuspid area. The sounds were clear and distinct. The rhythm was irregular in that every third beat was dropped. The blood pressure was 140 systolic and 90 diastolic. Examination of the abdomen disclosed the liver border 4 cm. below the right costal margin. Shifting dullness was elicited. There was a small umbilical hernia. The external genitals were normal. The cervix was bilaterally lacerated. The uterine fundus showed subinvolution. No adnexal tenderness nor masses were found. The extremities showed pitting edema two-thirds of the way to the knees.

Laboratory Work. Urinalysis showed specific gravity 1.013, albumin heavy trace, infrequent coarse granular casts. A concentration test on February 16, 1934, showed ability to concentrate to 1.013. Phenolsulphonephthalein output on January 9, 1934, was 10 per cent in two hours. Addis count (catheterized) on February 21, 1934, showed 462,000 red blood cells and 63,000 casts. Examination of the blood showed red blood cells 5,180,000, white blood cells 8,250. The differential formula

was normal. Non-protein nitrogen was 35, urea nitrogen was 18, creatinine 1.3 mg. per cent. The Wassermann was negative. Blood cultures (three) were negative. An electrocardiogram on February 10, 1934, showed 3:1 partial heart block (digitalis), and moderate left ventricular preponderance. On February 19, 1934, the block had disappeared. A teleoroentgenogram disclosed a transverse diameter of the chest of 24.4 cm., a transverse diameter of the heart of 17.0 cm.

By February 14, 1934, the albuminuria had disappeared and the blood pressure had dropped to 120 systolic and 80 diastolic and remained in normal range. The phenolsulphonephthalein output gradually increased to 35 per cent in two hours on January 19, 1934. The edema gradually disappeared and the patient felt well subjectively. The nocturnal dyspnea disappeared and the patient signed her own discharge on February 25, 1934.

*Case 10.** J. N., a colored sextipara, aged 31 years, had no knowledge of her illness until a routine examination while four months pregnant revealed high blood pressure. There were no symptoms until the ninth month, when blurring of vision and vertigo developed. Dyspnea occurred only on unusual exertion. Twins were delivered at term without instrumentation. There were no postpartal symptoms suggestive of sepsis and she remained in bed two full weeks. Twenty-five days postpartum paroxysmal nocturnal dyspnea developed. Dyspnea on slight exertion became evident and dependent edema appeared. Previous pregnancies had been entirely asymptomatic. Physical examination disclosed a blood pressure of 200 systolic and 128 diastolic, the typical retinal findings of diastolic hypertension, "hard exudate," arterial narrowing and irregularity, venous compression and beginning macular star in the left eye. The heart was enlarged, P_2 was accentuated, a systolic apical murmur and protodiastolic gallop rhythm were present. Basal râles, enlargement of the liver, dependent edema and elevated venous pressure were easily demonstrable. The urine disclosed a slight trace of albumin, an occasional fine and coarse granular cast and no red cells. Concentration reached 1.018 by the Fishberg technic. The Wassermann was negative. Electrocardiograms disclosed slurring of R_1 and R_2 and inversion of T_1 and T_2. Routine care with rest and digitalis cleared the patient of signs of congestion. Heart size remained unchanged.

Nephritic Group

Inspection of Case Reports 1 through 7 will disclose the diagnostic criteria for diffuse hemorrhagic nephritis, including significant hematuria, albuminuria, casts and edema, coupled with vascular changes and evidence of renal insufficiency. In addition to these findings, peculiar to all diffuse hemorrhagic nephritis, there are striking similarities in these cases in their relationship to the puerperal state. Each patient had been followed in the prenatal clinic with histories, physical examinations, repeated blood pressure determinations, and urinalyses. In no instance was there evidence of vascular or renal disease antepartum. Clear evidence of sepsis invariably appeared within five days following delivery and in two to three weeks, typical acute diffuse hemorrhagic nephritis was evident.

Nephritis in pregnancy, especially its relationship to and differentiation from toxemias peculiar to pregnancy, has long been a major problem. Clarification is progressing, especially since the introduction into the problem by recent investigators of the more satisfactory classifications of Bright's diseases. Reports of cases classified in this way are confined

* This case has been reported previously in Trans. Assoc. Am. Physicians, 1937, lii, 198.

chiefly to the antepartal period, and reports of nephritic symptoms arising postpartum without objective antepartum manifestations are extremely difficult to find. In those that do exist, the relationship to pregnancy is not described.[1, 2] The more important papers and monographs[3, 4, 5] on nephritis do not recognize nephritis dependent on a complication of the puerperium and occurring as a sequel to that complication.

In these seven patients, a relationship to the delivery is not undeniably established. The sequence of events—presumably normal patient, delivery, evidence of sepsis, usual latent period between sepsis and nephritis, followed by the development of nephritis—is highly suggestive. There remains to be shown the nature of the puerperal septic process and its relationship, if any, both to the delivery and to the nephritic manifestations.

A relationship of sepsis to nephritis has long been suspected and postulated. Although the etiology of diffuse hemorrhagic nephritis is unknown, its close and frequent association with streptococcal diseases, such as tonsillitis, scarlet fever, bacterial endocarditis (aside from embolic nephritis) suggests this organism as the etiologic agent. In addition, the streptococcus is intimately associated with puerperal morbidity and is almost singly the cause of grave puerperal sepsis. Since this organism is concerned both with puerperal sepsis and hemorrhagic nephritis, and since both these processes were apparent in our patients, the answer to the pathogenesis of the clinical picture may lie in a study of this organism.

Bacteriologic studies to disclose the presence of the streptococcus immediately suggested themselves as means of confirmation. We isolated this organism from the uterine secretions only once in seven cases, a frequency not differing from the incidence of positive cultures in the absence of nephritis.[6] These cultures were made from the cervix two to three weeks postpartum, at a time and a site where one would not necessarily expect to find the causative organism. Parametritis and endometritis, both commonly occurring postpartum without localizing signs,[7] may have acted as deep-seated streptococcal infections in the presence of negative cervical cultures.

Nephritis following streptococcal infections usually occurs seven to 14 days after the onset, except in scarlet fever, when it may occur as late as the twenty-first day. In our seven cases, the earliest manifestations which can be interpreted without doubt as nephritic range from 12 to 24 days postpartum. From the fever, interpreted as postpartal infection, the period of latency ranged from 12 to 21 days in all cases except in Case 6, in which symptoms of nephritis appeared 22 days following the first signs of urinary tract infection. If any signs of genital tract infection occurred, they were masked by those of the pyelitis and the time interval may be too long. Clinically, this period of latency, approximately three weeks, from signs of postpartal infection until the development of nephritis, is extremely significant evidence of a direct relationship, particularly since, in all other cases of hemorrhagic nephritis entering the wards during the same interval, there

was no close relationship to pregnancy and no cases occurred which would produce a continuity of days of latency above 22, a distinct break occurring from 22 days to eight months postpartum.

Age, parity and the type of delivery appeared to have little to do with the clinical picture. Six of the patients were below 26 years of age; the seventh was 38. Four were primiparae. Two were forceps deliveries, one an abortion, and four delivered spontaneously under aseptic technic in the Charity Hospital.

The outstanding difference between the clinical picture in this group and in nephritis unrelated to pregnancy was the prominence of diastolic hypertension and its symptoms. While hypertension is a prominent symptom in all acute glomerular nephritis, the findings in the present group were uniformly outstanding, and often, along with cardiac symptoms, dominated the entire picture. In patients 2 and 5 it appeared to be responsible for the heart failure. Reduction in pulse pressure, protodiastolic gallop rhythm, cardiac dilatation and accentuation of P_2 are representative of the cardiac manifestations. Low voltage and T-wave inversion characterized the electrocardiogram. These cases resemble closely the non-nephritic group and have, at times, caused some difficulty in differential diagnosis. In Cases 1, 3, 4, 5 and 7, hypertension was responsible for the marked cerebral symptoms, manifested in the first two by severe headache, and in the latter three by twitchings and convulsions.

Important in differential diagnosis are chronic nephritis and toxemias peculiar to pregnancy. Pyelonephritis and infected hydronephrosis are easily differentiated and cause no confusion. As may be seen in Case 6, however, both nephritis and infected hydronephrosis may occur together and the recognition of both diseases is important. Eclampsia, or preëclamptic toxemia, after labor with no evident signs before or during labor is unusual, but does occur. The older literature records numerous cases past the tenth day, but in modern diagnosis eclampsia past the tenth day is unknown.[8] In the present group, the onset is far beyond this time limit.

Chronic nephritis is singular in its tendency to manifest itself with exacerbations during the antepartum period. Such patients usually improve after labor when the strain of pregnancy is relieved. At the very time when we see symptoms developing in these patients, the nephritis would probably be receding. In all our cases prenatal examination disclosed no evidence of nephritis and the clinical findings and laboratory data, when the clinical picture developed, were in the main those of fresh disease. In two cases only was there evidence of streptococcal disease, tonsillitis, years before. Were these two patients examples of exacerbations of a nephritis present years before, their general features and relationship to pregnancy remain unaltered.

We have also seen focal nephritis at this time, but the presence of edema and hypertension, as well as urinary findings, rules out focal disease.

Non-Nephritic Cardiovascular Group

Cases 8, 9 and 10 are representative of the group characterized by cardiovascular symptoms and signs postpartum in the absence of demonstrable hemorrhagic nephritis. Eight patients of this type have been seen in our colored female services in the past three years. In the past 10 years many such patients have been seen. Data on such patients have been published from the Charity Hospital by Herrmann and King [9] in 1930 and by Hull and Hafkesbring [10] in 1937. Although the histories in Cases 8 and 9 reveal no subjective findings antepartum, we had not observed the patients at that time and cannot rule out the possibility of a latent process or objective evidence of disease antepartum. Case 10 had definite evidence of a hypertensive state antepartum, but no evidence of broken cardiac compensation. We have seen an occasional patient of this type who, when followed antepartum, has had evidence of hypertension, or at times other etiologic agents causing heart disease with mild congestive symptoms near term. Usually, however, an etiologic agent causing heart disease and evidence of heart disease have not been demonstrable antepartum. Postpartum diastolic hypertension has often been present.

In pregnancy, strain upon the heart increases progressively to, and reaches its maximum during, labor [11] with a release of strain following labor. The frequency of heart failure in pregnancy parallels the strain, and rarely does one find heart failure beginning postpartum except in the presence of some serious vascular accident.[12] Yet, in the present group of patients, within 18 to 25 days postpartum, evidence of left-sided then right-sided heart failure, with subsequent congestion of the kidneys, appeared in the absence of demonstrable serious vascular complications. The criteria necessary for the diagnosis of hemorrhagic nephritis were absent.

Symptoms have invariably developed within one month postpartum. Sudden dyspnea, cardiac dilatation, accentuation of P_2, tachycardia, development of gallop rhythm, low pulse pressure, pulmonary congestion and subsequent peripheral edema have characterized the clinical picture. At times the onset was gradual. Edema has often been the first symptom. It usually progressed to a marked degree, as in the three cases cited, with fluid in the serous cavities. Marked edema, together with cardiac enlargement, protodiastolic gallop rhythm, high diastolic and low pulse pressure were the outstanding diagnostic clinical findings. It is to be recalled that these findings were also present in certain patients in the nephritic group. Such patients with both nephritic and cardiac states may rightfully fall into both groups, and the archaic term " cardiorenal " seems appropriate. The electrocardiographic changes, previously mentioned, were also similar.

Data at present are too meager to state the effects of parity and obstetrical complications. Patients 8, 9 and 10 had had 11, 3 and 3 children, respectively. In all instances, previous pregnancies had produced no similar illness. There were two instances of twins, however, and one of toxemia of pregnancy.

The outcome in general has been good. Indeed, in the non-nephritic group we have witnessed no deaths and can report no autopsy findings. However, Gouley, McMillan and Bellet[13] have recently reported four cases of this type representing the fatalities in seven such patients. All had serious vascular complications. Necropsy showed "a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease." The lesions were focal, showing acute and subacute phases of myocardial disintegration with hemorrhage and a cellular infiltration. Older lesions showed fibroblastic activity leading to acellular scar formation.

Treatment in our hands has consisted of the routine measures employed in congestive failure—bed rest, digitalization, fluid restriction, diuretics, venesection, mechanical removal of fluids from serous cavities, and symptomatic measures. Response to treatment was not striking and, as a rule, gradual improvement resulted in restoration to activity in several weeks, with reduction of blood pressure to normal range. An occasional patient, such as Case 10, becomes a chronic cardiac invalid with readmission to the ward at irregular intervals for bed rest.

We have emphasized the marked cardiovascular symptoms noted in the first seven cases. These findings often dominate the clinical picture and have in our experience led to confusion between these two groups. It is very likely that the factors responsible for the prominence of the hypertensive and cardiac symptoms in the nephritic group play a part in the development of cardiac failure in the non-nephritic group. In both groups the occurrence of cardiovascular symptoms postpartum is significant and the relationship to pregnancy and the puerperium requires further study. That acute hemorrhagic nephritis may cause such a picture when not postpartal is well known, even to the extreme electrocardiographic changes indicative of cardiac involvement.[14] However, the extent and severity of the symptoms were so striking, and the elevation of blood pressure so uniform, that when considered with similar manifestations in the non-nephritic group, the possibility of some force or forces, unknown or idiopathic, directly related to pregnancy, a "postpartal cardiac factor," seems worthy of careful consideration. There may be present an injurious influence or the lack of a helpful factor. According to older medical traditions, a toxin would be suspected. Endocrine or vitamin factors are more likely according to present fashions of thinking. This possibility is further strengthened when we note that similar breaks in cardiac compensation have occurred at similar intervals following pregnancy in women in whom rheumatic and hypertensive heart disease were known to be present, but compensated, before delivery. It appears that a puerpera whose myocardium is already subjected to a strain may, for reasons peculiar to the puerperal state, be precipitated into cardiac failure. The myocardial strain may consist of a previous event or occur *de novo*. If new and transitory, as the hypertension of acute nephritis often is, complete clinical recovery may follow.

The factors peculiar to the puerperal state are unknown. The low voltages seen in the electrocardiogram of patient 8 and the T-wave changes in Cases 8 and 10 have led to the suggestion of " toxic " heart disease. We know of no toxin to cause it. The studies of Gouley et al., however, demonstrate anatomic changes of a distinctive character, unlike those seen in the usual etiologic types of heart disease, and further strengthen the theoretical consideration of a factor peculiar to pregnancy and perhaps to certain other states, for in two cases similar findings were demonstrated in the male.

The frequency of diastolic hypertension in these patients as well as similar cardiac findings in the patients with hypertension of acute nephritis indicates that hypertension may be a factor in the development of this clinical picture. It is important to remember, however, that all patients do not have hypertension. We agree with Gouley, McMillan and Bellet that the clinical picture and the histological findings reported by them are not those of the chronic hypertensive state. That hypertension may contribute to the clinical picture as a precipitating factor is evident.

Aside from the few factors mentioned, many other changes may occur in the ante- and postpartal periods, either as usual or unusual events, and contribute to the cardiac disability seen in the non-nephritic group. The marked changes which take place in endocrine functions at this time suggest themselves as possibilities. One may recall the relationship of the pituitary gland both to the puerperium and to arterial hypertension. Ovarian insufficiency has been linked up with venous hypertension. Villaret, St. Girons, and Grellety-Bosviel [15] reported venous hypertension (16 to 35 cm. of water) and cyanosis in patients said to have had ovarian insufficiency. While the changes in ovarian function occurring at and after labor might contribute to such a picture, it could hardly be more than a partial explanation. Stieglitz [16] has shown that in the puerperal period, coincidental with the onset of lactation, there occurs an increase in arterial tension in both normal and abnormal patients. These changes occur with a diminution in blood calcium, but the causal relationship between the two is unknown. This influence upon the blood pressure is probably responsible in part for the prominent cardiovascular symptoms in these patients. Metabolic changes, anemia, and vitamin deficiency may occur. Infection may be debilitating. Unknown factors may be important. One must realize as well that the pregnant woman usually curtails her physical activities. Labor, to be sure, adds a great strain, especially to the primipara. This is sudden and followed by a period of only partial activity. The period at which full exercise is usually resumed agrees closely in time with the period in which cardiac failure was precipitated in our cases and may have been an important precipitating factor.

The etiology of this group remains obscure. That some process peculiar to the puerperal state may at times act as a precipitating cause of failure in hearts otherwise damaged, or that the same process, together with other changes which contribute to cardiac strain, such as hypertension and mal-

nutrition, may act together and produce failure in a previously normal heart are possibilities which remain unanswered at present.

Summary

Two late puerperal complications, following an interval of apparent health, have been recognized: (1) Acute hemorrhagic nephritis. Patients without evidence of disease until the puerperal period, developed within three to five days following delivery signs of sepsis followed in 14 to 21 days by the appearance of typical acute diffuse hemorrhagic nephritis. (2) Congestive heart failure. These patients showed previous to delivery little or no evidence of cardiac failure, but 14 to 25 days postpartum developed frank cardiac failure. Possible relationships of both of these groups to labor and the puerperal state have been pointed out.

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POSITIVE PRESSURE RESPIRATION AND ITS APPLICATION TO THE TREATMENT OF ACUTE PULMONARY EDEMA *

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The purpose of this paper is to present observations we have made which provide a physiologic basis for the use of positive pressure respiration in the treatment of acute pulmonary edema. For the most part positive pressure has been thought of as a method of resuscitation such as that accomplished by the pulmotor in accidental asphyxia. The function of pressure in the respired air has, however, a broad physiological significance, being employed by the human organism itself as a compensatory mechanism as well as lending itself to therapeutic application in inhalational therapy. We wish to present the subject from the following points of view: (1) A critical discussion of the pertinent literature. (2) Animal experimentation on the development and treatment of acute pulmonary edema. (3) Physiological studies on the effect of positive pressure respiration in human subjects. (4) The clinical results of treatment with positive pressure in patients with acute pulmonary edema.

1. Discussion of Literature

In 1878 Welch [1] presented his theory of the origin of pulmonary edema in the following words: "A disproportion between the working power of the left ventricle and of the right ventricle of such character that the resistance being the same the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." By squeezing the left ventricle of rabbits between his fingers, Welch observed in many instances forcible contraction of the right ventricle with diminished force of the left ventricle, as indicated by the pressure in the carotid artery, with the result that well marked pulmonary edema took place.

Meltzer [2] brought apparent confirmation to this hypothesis by producing pulmonary edema in rabbits through the intravenous injection of adrenalin. He explained this occurrence as a result of the considerable constriction of the smaller systemic blood vessels, which presented such an increased burden to the left ventricle that it became unable to expel all the blood which it received from the pulmonary veins, while on the other hand the right ventricle unloaded with increased energy upon the lungs all the blood which the contracting vessels drove into it.

Haven Emerson [3] in 1909 showed that pulmonary edema produced by adrenalin could be consistently removed by applying artificial respiration

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through a tracheotomy tube, gently distending the lungs and allowing them to collapse. The explanation he advanced for the striking improvement in respiration and circulation which occurred was that the full expansion of the lungs due to distention from within forced a considerable amount of blood onward to the left auricle and ventricle; during expiration more room in the pulmonary vessels and a diminished resistance in the lungs allowed the distended right ventricle successfully to empty itself. He suggested as a clinical procedure artificial respiration, raising the arms of the patient above the head and then pressing them across the upper part of the abdomen, believing that this accessory pumping action would facilitate the flow of blood through the lungs.

This suggestion was tried several weeks later by Barringer,[4] in a patient with cardiac insufficiency who suddenly developed edema of the lungs. At the end of an hour of artificial respiration the signs of edema, rattling in the throat and moist râles had largely disappeared.

In 1897 Norton[5] had reported a case of edema of the lungs due to carbolic acid poisoning in which a rapid clearance of the edema took place with the use of the Fell-O'Dwyer forced respiration apparatus. Although a theoretical discussion of the mechanism was not made in this report, the clinical result was carefully described and was unmistakably the result of the introduction of a laryngeal tube and the application of forced respirations under positive pressure. (Description of apparatus published by Northrup.[6])

The use of positive pressure as an aid to breathing is described in even earlier literature. Oertel (1878)[7] employed 20 to 100 inspirations of air compressed to $\frac{1}{80}$ to $\frac{1}{50}$ atmosphere excess pressure in the treatment of severe asthma, and remarked that the dyspnea is relieved while the inflation of air cells is checked by the cessation of the forced inspiratory movements and the rarefaction of air within them prevented. He also had traced the secretion of sero-mucous fluid into the finer bronchi to the violent inspiratory dilatation of the thorax during occlusion of the bronchioles; a concept which our own studies appear to confirm.

The observations of Emerson as to the effectiveness of artificial respiration in abolishing pulmonary-edema due to adrenalin were confirmed by Auer and Gates in 1917[8] and by Johnson.[9] Auer and Gates also showed that tracheal stenosis accentuated the edema caused by adrenalin. When adrenalin was injected in rabbits whose hearts were exposed for inspection and in whom artificial respiration was carried out, they observed the pulmonary artery to be dilated, the left auricle enormously swelled, the left ventricle small, and sooner or later the rate of contraction of the left ventricle became only half that of the right side of the heart. However, despite the apparent fulfillment of the fundamental postulate of Welch's theory, the degree of pulmonary edema produced was slight and even negligible when compared with the marked edema which resulted from the same dose of adrenalin injected into animals whose thorax was intact. Even more

striking edema was produced when the vagi had been divided. The authors rejected Emerson's tentative explanation that distention of the lung by artificial respiration drove a considerable amount of blood into the left auricle and thus relieved the pulmonary congestion, nor did they believe that the edema resulted from back pressure from the left ventricle, since they did not observe any dilatation of the left ventricle or regurgitation in the left auricle. The left ventricle in the rabbit after adrenalin seemed to be in a state of greater tone than normal. They believed that artificial respiration with positive pressure did not exert its inhibitory action on pulmonary edema through action on the heart itself, but that the significant factor involved was the relief of the negative pressure within the chest which exerted a suction action, like dry cups, on capillaries in the alveolar walls.

Although adrenalin relieves bronchial asthma, it had been shown by Golla and Symes [10] that adrenalin in animals produces constriction of the bronchioles unless previous constriction has been produced by other drugs. Since constriction of the bronchial muscles had been experimentally demonstrated as a result of adrenalin injection, Auer and Gates assumed that an increased negative pressure within the chest became necessary during inspiration, producing the cupping action on the alveoli which aided the passage of fluid from the engorged capillaries into the alveoli.

According to these authors, the positive pressure which artificial respiration produced in the lung partially overcame the bronchial constriction due to adrenalin and thus prevented the intra-alveolar pressure from becoming highly negative during inspiration, in that way removing the suction action on the pulmonary capillaries.

Loeb [11] in reviewing the evidence just presented came to the conclusion that the reduction of the negative pressure due to insufflation of air into the lung was the important factor in the prevention or amelioration of pulmonary edema produced by adrenalin.

Plesch [12] also made the suggestion that increased pressure in the air passages of the lungs would be valuable in the treatment of pulmonary edema. He mentioned that the effect would be to push the blood already in the pulmonary circuit onwards to the left ventricle and at the same time to oppose the delivery of more blood by the right ventricle; he believed it would be of special importance when the patient's respiration was " rattling," for this was considered by him to be a compensatory mechanism to hinder the edema; the patient makes short inspiratory gasps since the diminished pressure during inspiration is dangerous, tending to cause edema and makes prolonged rattling expirations through the bronchi and glottis which keep up a pressure acting in the opposite direction.

Poulton [13] reported beneficent results from the use of this technic in some cases of paroxysmal dyspnea (" cardiac asthma ") and in bronchial asthma, although no benefit was obtained when there was generalized heart failure.

The production of congestion and edema of the lung as a result of tracheal stenosis was shown by Moore and Binger [14] to be due to the obstruc-

tion during inspiration, for these changes did not take place during expiratory obstruction alone. Barach [15] confirmed these observations and also showed that expiring against a positive pressure created no significant changes in the lung, whereas inspiring against a negative pressure caused congestion and edema, particularly in the lower parts of the lung and areas of emphysema at the periphery. In animals breathing through constricted orifices the negative intrapleural pressure increased as high as tenfold the normal value during the course of a six-hour experiment but when respiration was conducted under a positive pressure of 5 cm. of water, a substantial reduction in the negative intrapleural pressure took place. This was more marked when a helium-oxygen mixture, in which the density was one-third that of oxygen, was employed.

The effect of increased negative pressure on the pulmonary blood flow has been the subject of considerable study, the literature having been reviewed by Tigerstedt [16] and by Wiggers.[17] Daly [18] showed that expansion of the lungs in animals, accomplished by a negative pressure chamber, resulted in an increased pulmonary and peripheral blood flow. Mollgaard,[19] in experiments on the whole animal found similar results. It appeared, therefore, that even relatively marked expansion of the lungs decreased the resistance of the pulmonary bed. When inspiratory obstruction was produced in the cat, Huggett [20] found that a marked increase in the minute volume of the heart took place, whereas expiratory obstruction caused the reverse, the blood flow being determined by the Ficke principle.

The sequence of events in the production of pulmonary congestion and edema due to tracheal stenosis may now be postulated as follows: There is an immediate increase in the negative intrapleural pressure which becomes progressively greater. The resistance of the pulmonary bed is lessened and there is at first an increase in the pulmonary and peripheral blood flow. An additional factor promoting increased filling of the right heart may be dilatation of the right auricle. As the intra-thoracic negative pressure increases, blood continues to enter the lungs through the right ventricle but the passage of blood through the lungs into the left auricle and especially from the left ventricle into the extra-thoracic aorta is hindered by the high negative chest pressure. A progressive accumulation of blood in the lungs follows, with a consequent increase in the capillary blood pressure causing a greater filtration pressure outward. Finally, the physical effect of a pathologically heightened negative pressure in the chest exerts a suction action on the capillaries resulting in an exudation of serum into the alveolar walls and spaces, and into the bronchiolar structures as well.

In another group of cases, pulmonary edema may be caused by an increase in permeability of the capillaries to edema fluid. Landis [21] found that when capillaries are deprived of oxygen for three minutes their permeability to protein is increased. Krogh [22] showed experimentally that dilatation of a capillary also increases its permeability. Since anoxemia and pulmonary engorgement are both frequently present in conditions in which pulmonary

edema may occur both these factors may participate. When pulmonary edema is caused by irritant gases such as chlorine in commercial plants and to phosgene in war gas poisoning, the pathogenesis of edema of the lungs may be traced directly to increased permeability. Pulmonary edema as a complication of pneumonia is probably in large part due to an increase in capillary permeability caused by inflammation, probably similar to the irritant inflammation of poisonous gases. However, in many patients with pneumonia the condition is complicated by left as well as right ventricular failure and it is at times difficult to say whether cardiac failure followed pulmonary edema or whether it was present as a contributory cause. An attempt will be made in the clinical section of this paper to analyze the various factors that may have been involved in individual cases of edema of the lungs.

In previous reports dealing with the effect of helium-oxygen mixtures in asthma and respiratory obstruction, Barach [23] pointed out that the use of positive pressure decreases the effort necessary for inspiration and that in patients with asthma the existence of positive pressure during expiration maintains a backward distending pressure which keeps open bronchial and bronchiolar structures that physiologically constrict during the expiratory cycle. This observation suggested the explanation of why patients with asthma and emphysema so frequently pursed their lips during expiration and arbitrarily increased the resistance to the egress of air. This mechanism, developed by the patients themselves, appeared to have the physiological advantage of keeping open bronchiolar passageways, thereby producing a more efficient emptying of the alveolar air. It was suggested that the expiratory grunt in lobar pneumonia was a similar protective mechanism. Furthermore, it was found that patients with more or less continuous asthma of moderate degree will frequently obtain marked relief of their wheezing when they follow the instruction to breathe through partially closed lips for 3 to 10 minutes. The râles in expiration will at times clear up immediately, apparently due to distending the bronchioles through internal pressure. This observation provided an additional stimulus to employ positive pressure respiration in the treatment of acute pulmonary edema; we reported in a preliminary communication three cases in which a swift clearance of the moist râles in the chest took place, even in the presence of advanced circulatory deficiency.[24]

Since congestion and edema do not occur as a result of expiratory obstruction but consistently follow inspiratory obstruction, the use of positive pressure respiration receives additional support in the treatment of dyspnea due to obstruction. Inasmuch as excessive pressures would obviously prevent the entrance of an adequate amount of blood into the right heart, it was cautioned that this procedure should be followed only with the careful use of manometric readings of the pressure of the respired air.

In the review of the literature above, an essential factor in the production of pulmonary edema, due either to adrenalin or to tracheal stenosis, appeared

to be a heightened negative pressure within the chest exerting a direct suction action on the capillary wall. It is of some interest at this point to remember that Graham [25] suggested that the swift formation of pleural exudates in influenzal broncho-pneumonia might be due to a negative pressure within the chest produced by the attempt to inflate the lung through smaller bronchial passages that were constricted by inflammatory swelling.

In the earlier communication [24] we reported the rapid clearance of acute pulmonary edema as the result of the continuous application of positive pressure during the total respiratory cycle. Before reporting these results in detail it was thought advisable to study the mechanism more carefully. Although the sequence of events in the production of pulmonary edema following tracheal stenosis seemed clear from the physiological data described above, the type of edema associated with circulatory failure was less easily explained. It seemed likely that additional light could be thrown on the pathological physiology of pulmonary edema due to left ventricular failure if more careful observations were made on experimental edema of the lungs in rabbits due to adrenalin.

2. Experimental Observations on the Development and Treatment of Acute Edema of the Lungs Caused by Adrenalin

Rabbits were anesthetized with evipal intravenously for short experiments and ether by the open drop method in long continued experiments. Adrenalin was injected into the ear veins, the dosage employed being 0.5 c.c. of a 1 to 1000 solution per kg. body weight. Within 15 seconds after the injection the majority of animals stopped breathing for a period of 15 seconds to 2 minutes. In some instances the rabbit died during this period before the development of edema. Autopsy then revealed massive pulmonary congestion. When the animal began to breathe again the respiratory rate was extremely rapid and shallow and generally within 2 to 5 minutes pulmonary edema could be clinically recognized, either by palpation or auscultation. Before the death of the animal a foamy, frequently blood-tinged, fluid exuded from the nostrils. Autopsy of the latter animals showed widespread pulmonary congestion and edema. The heart was markedly enlarged, the enlargement being due to a marked dilatation of the right ventricle and auricle. The left auricle was usually moderately dilated. The left ventricle was contracted and showed no evidence of dilatation.

Data included measurements of the intrapleural and intratracheal pressures, the pulmonary ventilation and tidal air, the systolic arterial pressure, venous pressure, pulse and respiratory rates. A total of 100 rabbits were used. All determinations could not be obtained simultaneously on each animal but there were at least 10 observations on each measurement described. A spirometer of small diameter, namely 5.08 cm., was built in order to show recognizable oscillations of the tidal air and measure the pulmonary ventilation of the rabbit. Each millimeter rise in the bell represented a volume

change of 1.96 c.c. A high speed drum was used to record graphically the changes in chest pressures as well as the respiratory tracings.

The arterial pressure was obtained by inserting a needle into the femoral artery and connecting it with a long glass tube containing saline with a small amount of oxalate solution. Venous pressure was measured in a similar way using the femoral or ear veins. Graphic recording of the intrapleural and intratracheal pressure was made possible by a delicate float with an attached pen suspended in a water manometer.

The roentgen-ray pictures were made possible by a special technic used by Dr. Ross Golden in which films could be taken at 10 to 15 second intervals. The rabbits were tied to a board and pictures taken before and at various intervals after injection and after application of positive pressure respiration.

A series of roentgen-ray pictures taken at 15 second intervals after intravenous injections of adrenalin revealed a progressive increase in the size of the heart shadow. This increase was observed as early as 10 seconds after the injection. In the accompanying reproduction (figure 1) it will be seen that the largest transverse diameter of the heart increased from 3.5 cm. before adrenalin to 3.8 cm. one minute after and 4.1 cm. three minutes after. In addition the lung field became progressively darker, indicating the development of pulmonary congestion and edema.

In figure 2 the size of the heart is shown after adrenalin, and after adrenalin with positive pressure. The rabbit was given the usual dose of adrenalin intravenously and the first picture taken one minute later. Positive pressure was applied immediately thereafter by intermittent inflation of the lungs at a rate of 36 times a minute. The lung was expanded by a pressure of 8 to 10 cm. of water, the trachea being connected to a basal metabolism apparatus in which a positive pressure blower was used. The rabbit breathed 100 per cent oxygen in this experiment, although in the majority air only was employed. Expiration was allowed to take place passively. One minute after the injection, the transverse diameter of the heart increased from 3.3 cm. to 4.1 cm. After three minutes of positive pressure breathing, the heart size was slightly smaller, 3.9 cm. in transverse diameter. The animal was killed five minutes later. Considerable passive pulmonary congestion was found but no evidence of edema.

Figure 3 shows the effect of intermittent inflation of the lung superimposed on a continuously exerted positive pressure both during inspiration and expiration. The animal's trachea was connected with a motor blower unit which maintained a positive pressure of 4 cm. during inspiration and 6 cm. during expiration. Intermittent inflation was then added so that the animal experienced a pressure of 10 cm. during inspiration and 6 cm. during expiration. The first photograph shows the normal transverse diameter of the heart to be 3.4 cm. One minute after injection of adrenalin there is an increase to 4.0 cm. The combined intermittent inflation and continuous positive pressure was begun immediately after the second picture and the film taken three minutes later. This showed a marked decrease in the trans-

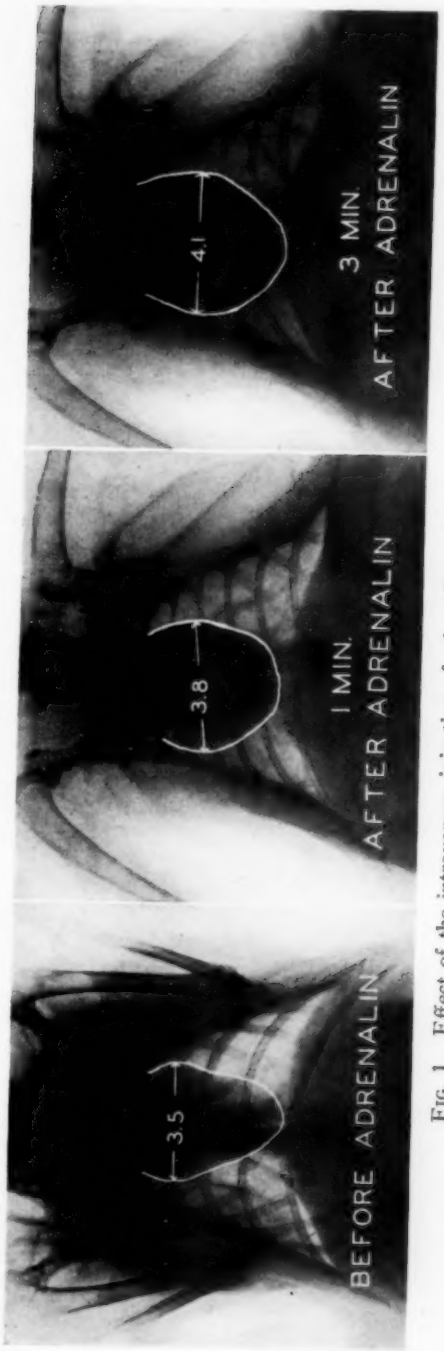


FIG. 1. Effect of the intravenous injection of adrenalin on the size of the rabbit heart.

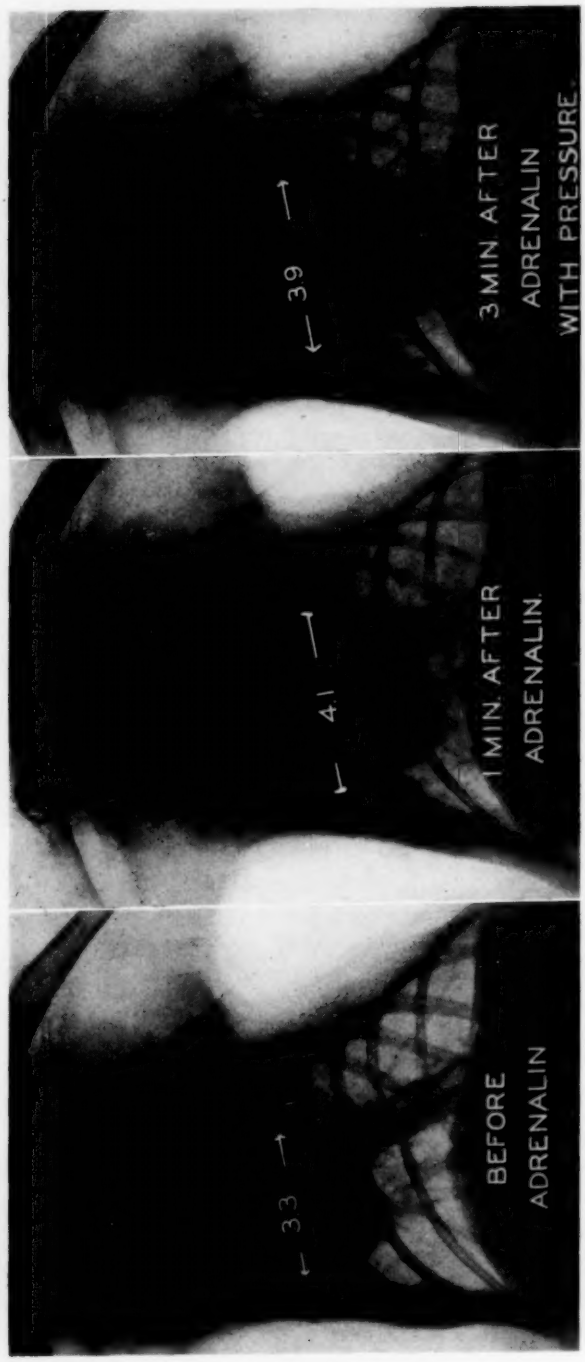


FIG. 2. Effect of intermittent inflation of the lung on the size of the rabbit heart after adrenalin.

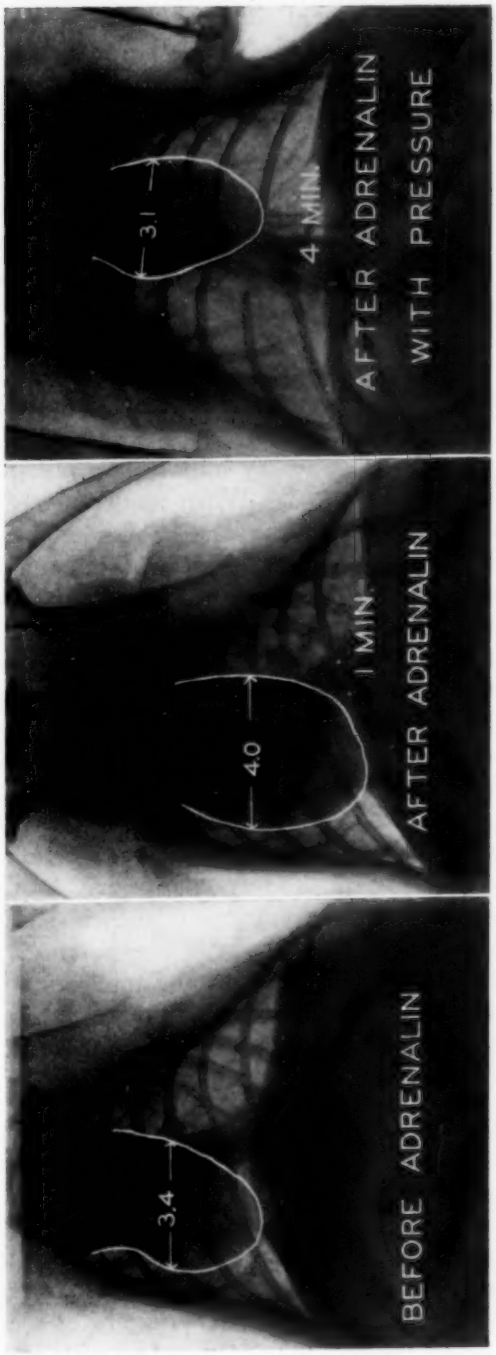


FIG. 3. Effect of positive pressure on the size of the rabbit heart after adrenalin.

verse diameter of the heart to 3.1 cm. It will also be observed that the lung was expanded, the diaphragm flattened, and the lung field showed an increased radiability. The animal died five minutes later possibly due to the maintenance of excessive pressure interfering with an adequate inlet of blood into the right heart. At autopsy, however, pulmonary congestion and edema were not found.

The three pictures reproduced above illustrate the significant findings obtained by roentgen-ray of the heart. We may summarize these results as follows: Following the intravenous injection of 0.5 c.c. of adrenalin per kg. of body weight, there is a marked increase in the transverse diameter of the heart within 15 seconds. A further progressive increase takes place, reaching a maximum at approximately three minutes after injection. At this time a darkening of the lung shadow, particularly at the bases of the lung, takes place.

When positive pressure is applied by intermittent inflation of the lungs, pulmonary edema may be prevented. When moderate pressures are used, the heart size appears to be slightly decreased. Under these circumstances autopsy shows a dilated right ventricle, passive pulmonary congestion of moderate extent, without edema. When more marked positive pressure is employed, such as is achieved by intermittent inflation of the lungs plus a positive pressure continuously exerted during expiration as well as inspiration, the heart size may become even smaller than it was during the control period. Under these circumstances pulmonary congestion and edema may be prevented. However, the animal may die, if excessive restriction of blood flow is maintained for a long period.

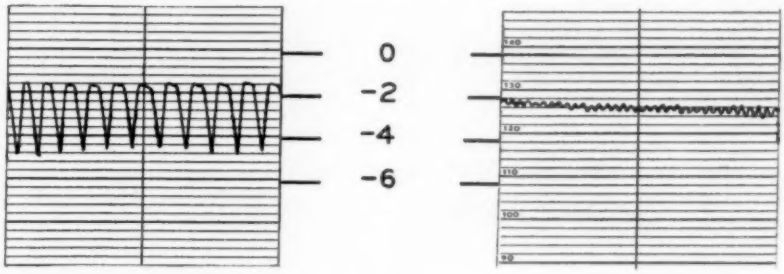
We have not attempted to determine in a precise way the optimal pressures required to control the onset of pulmonary congestion and edema, but have established the fact that pulmonary edema may be prevented by the application of positive pressure respiration of such a degree as to cause a slight diminution in the size of the heart. The possibility presents itself that cardiac dilatation may be controlled by the application of positive pressure respiration in which a decreased entrance of blood into the right heart is accomplished. The danger of an excessive curtailment of total blood flow must of course be kept in mind.

Respiratory Measurements after Intravenous Injection of Adrenalin in the Rabbit

Since it had been assumed that a pathologically elevated negative chest pressure was the important factor in the production of pulmonary edema [8, 11] it seemed desirable to make direct observations of the intrapleural pressure. In the accompanying graph, the intrapleural pressure of a rabbit before and after adrenalin is shown (graph 1). It will be seen that the intrapleural pressure ranged from approximately — 1.6 to — 4.4 cm. of water during the control period. After injection of adrenalin (1.2 minutes) the range

was exceedingly small, namely about 0.3 cm., the average pressure being —2.4 cm. The respiratory rate increased from 55 to 175.

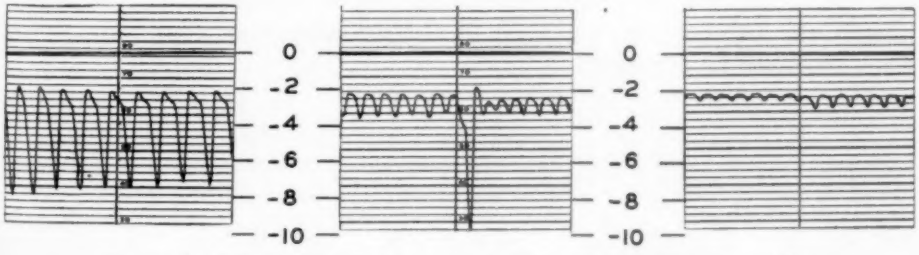
In graph 2, the intrapleural pressure of a rabbit is shown in which there is not only a decrease in the range of pressure but in which the average pres-



GRAPH 1. Effect of adrenalin on the intrapleural pressure of a rabbit.
Control
1.2 min. after adrenalin

sure between inspiration and expiration is even less negative than in the control period (graph 2). Thus, the mean negative intrapleural pressure is —4.9 cm. before injection of adrenalin, —2.8 cm. two and one-half minutes after injection and —2.6 cm. five minutes after injection.

The changes produced by intermittent inflation of the lung in a rabbit which had previously been injected with adrenalin are shown in graph 3.



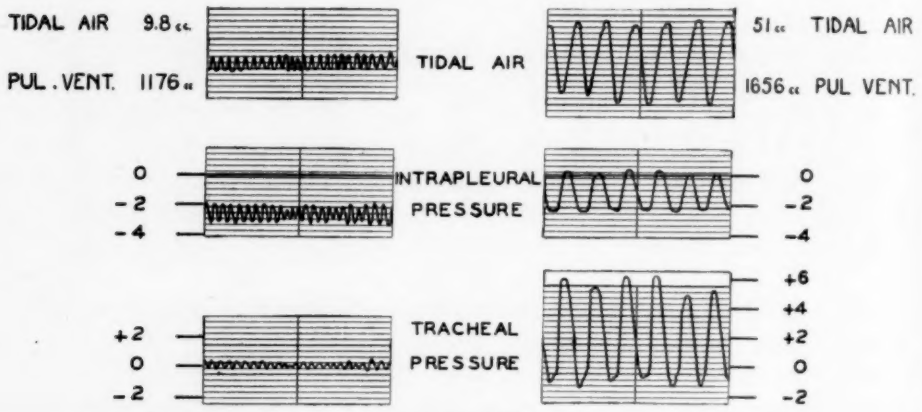
GRAPH 2. Effect of adrenalin on the intrapleural pressure of a rabbit.
Control
2.5 min. after adrenalin
5.0 min. after adrenalin

The tidal air was increased from 9.8 to 51 c.c., the pulmonary ventilation from 1176 c.c. to 1656 c.c., the intratracheal pressure from that of the atmosphere to as high as plus 6 cm. during the expanding or inspiratory cycle.

The intrapleural pressure rose (as a result of intermittent inflation) from a range of approximately —2.0 cm. to —3.2 cm. to a range of plus 0.2 cm. during inspiration and —2.3 cm. during expiration.

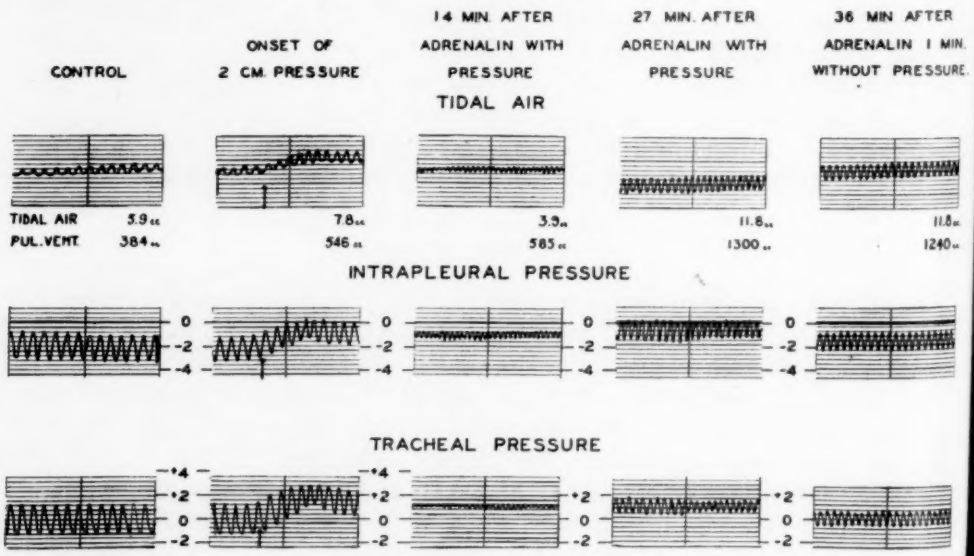
A detailed view of the effect of continuous positive pressure, without intermittent inflation, may be seen in graph 4. The control period shows a tidal air of 5.9 c.c. and a pulmonary ventilation of 384 c.c. After the onset

of a continuous pressure of 2.0 cm. of water throughout the respiratory cycle, the tidal air was 7.8 c.c. and the pulmonary ventilation 546 c.c. Adrenalin was then injected, with positive pressure continuing. The tidal air dropped to 3.9 c.c. 14 minutes later with a pulmonary ventilation of 585 c.c. Twenty-



GRAPH 3. Effect of positive pressure respiration on a rabbit after adrenalin.
Normal respiration
Positive pressure respiration

seven minutes after injection of adrenalin, the tidal air was 11.8 c.c. with a pulmonary ventilation of 1300 c.c. Thirty-six minutes after adrenalin and one minute after pressure was withdrawn, the tidal air was 11.8 c.c. and the pulmonary ventilation 1240 c.c. The animal was autopsied. Pulmonary edema was absent. There was only slight pulmonary congestion. The heart did seem to be dilated.



GRAPH 4. Effect of positive pressure on the respiration of a rabbit after adrenalin.

We may summarize the results just reviewed as follows:

The characteristic effect of the intravenous injection of 0.5 c.c. adrenalin per kg. of body weight on the respiration of the rabbit is an immediate and marked increase in rate, as high as 175 per minute. The tidal air becomes exceedingly shallow, dropping as low as 1 to 2 c.c. In many instances there is a temporary period of complete cessation of respiration. The extreme shallowness of respiration undoubtedly introduces an anoxemic factor, although measurements of the oxygen saturation of the arterial blood were not made. Since capillary permeability has been shown to be increased by anoxemia, this factor may play a rôle in the production of edema.[21]

The significant finding in these experiments is that concerned with the modification of intrapleural pressure. These observations demonstrate that no increase in negative pressure takes place in the intrapleural space as the result of the injection of adrenalin. Observations were recorded on 75 rabbits. The main effect was a consistent and marked decrease in the *range* of intrapleural pressure. The mean point between inspiration and expiration was approximately the same as that in the control period. A pathological increase in the negative intrapleural pressure was only found shortly before death, about 5 minutes after onset of pulmonary edema. At this time the tracheal tree was filled with foaming, blood-stained mucus, the animal resorting to powerful inspiratory gasps in order to suck air into his lung.

The effect of positive pressure whether applied continuously during inspiration and expiration or whether administered with intermittent inflation of the lung was to raise the intrapleural pressure so that it was atmospheric at one phase of the respiratory cycle and approximately — 2 cm. at the other phase.

Effect of Positive Pressure Respiration on the Systolic Arterial Pressure and the Venous Pressure in Rabbits after Adrenalin Injection

The systolic arterial pressure was measured by cannulizing the femoral artery and connecting it with a water manometer containing normal saline; the venous pressure was obtained in the same way. Fifteen rabbits were used. The procedure was similar to that employed in arriving at the previous measurements. Determinations were made on the systolic arterial pressure and the venous pressure before and after injection of adrenalin, with and without positive pressure. The results may be summarized in the following charts (charts 5 and 6).

In chart 5 it will be seen that immediately following the intravenous injection of the standard dose of adrenalin, a rise in systolic arterial pressure took place from 79 mm. Hg to 240 mm. Hg. (The pressure was measured in cm. of salt solution and converted into mm. of mercury by calculation.) The arterial pressure then declined, and, if the animal sur-

vived, approached the control level in 15 to 20 minutes. The course of a typical experiment is shown in the graph. The venous pressure generally showed a very slight rise, as shown in the graph, from 55.0 mm. of water to 65.0 mm. of water. If the animal died there was frequently a further rise of venous pressure of 10 mm. If the animal survived, the venous pressure fluctuated within a range of 10 mm. around the control level.

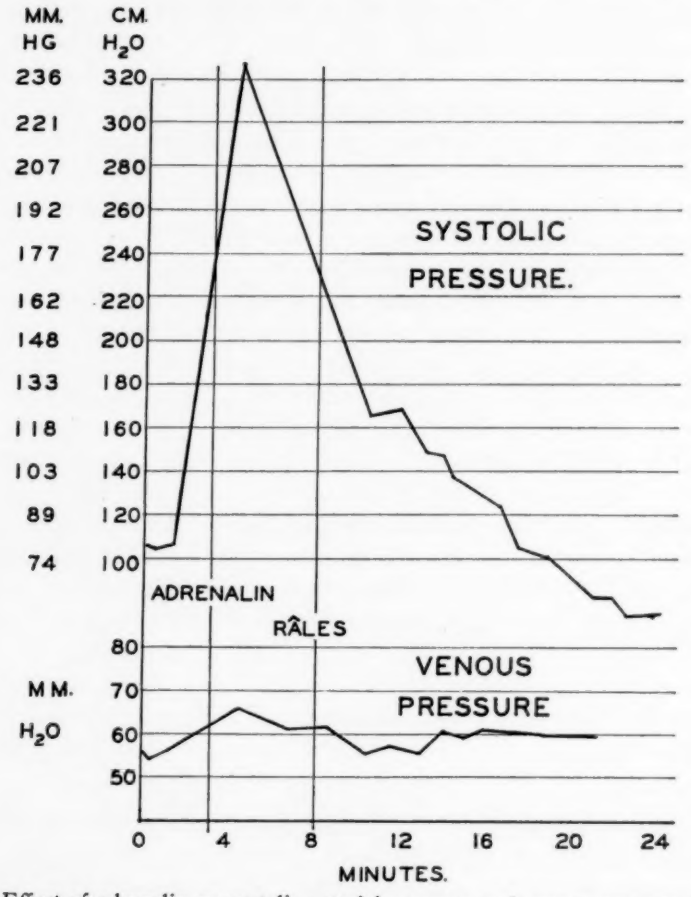


CHART 5. Effect of adrenalin on systolic arterial pressure and venous pressure of normal rabbit.

In chart 6 a graphic record is shown of a rabbit breathing under positive pressure, injected with adrenalin, and intermittently treated with positive pressure afterwards. It will be seen that positive pressure respiration of 4 to 6 cm. had no noticeable effect on the systolic arterial pressure either before injection of adrenalin or afterwards. The venous pressure likewise showed no effect when the animal breathed under 4 cm. positive pressure, but a slight elevation at times took place when the animal was exposed to a pressure of 6 cm. of water. The rise in venous pressure was generally no

greater than 8 mm. of water, and, *after injection* of adrenalin, this rise sometimes did not take place.

The marked rise in systolic arterial pressure, following intravenous injection of adrenalin, was the only noteworthy finding in these experiments. It is of interest that application of positive pressure respiration either by intermittent inflation of the lung, by continuous pressure during inspiration

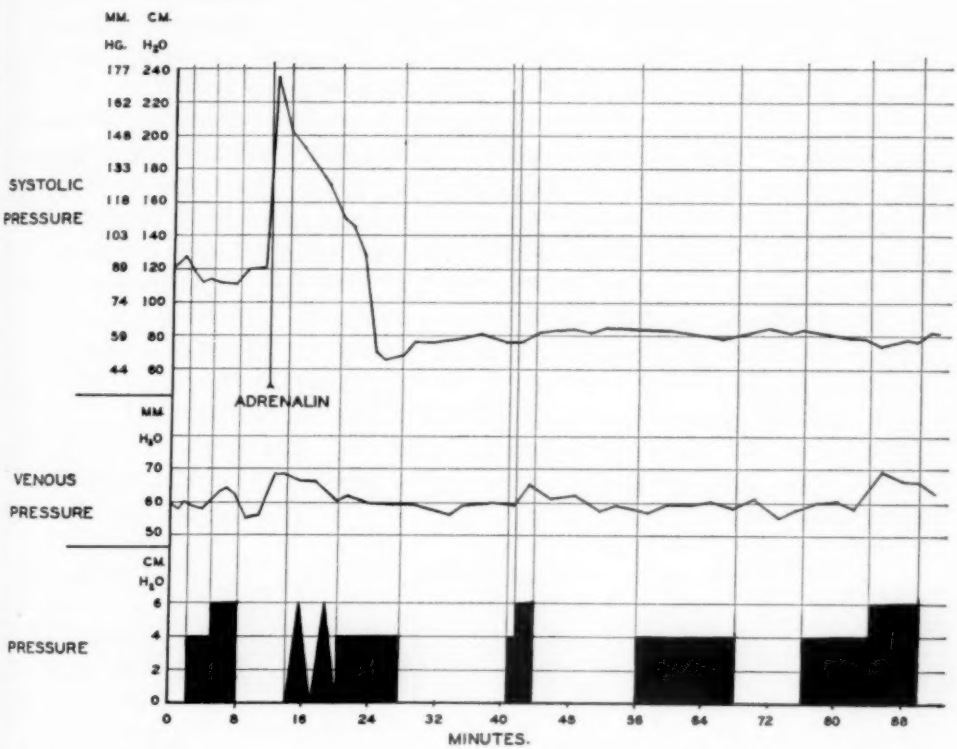


CHART 6. Effect of positive pressure respiration on systolic arterial pressure and venous pressure in a rabbit after injection of adrenalin.

and expiration, or by a combination of both methods did not consistently modify the arterial pressure. It should be borne in mind, however, that the dose of adrenalin administered was an exceedingly large one for an animal of this size and that the vaso-constriction produced in the systemic arterial system was probably maximal. It was also surprising that the venous pressure was so little altered, even by respiration under 6 cm. of water pressure. We are unable to account for this except on the basis of an increased volume output of blood into the lungs on the part of the dilated right ventricle and a consequent increased diastolic filling of the right heart.

We may now attempt to interpret the pathogenesis of acute pulmonary edema produced in the rabbit by intravenous injection of adrenalin. Our results confirm those of Auer and Gates [8] and of Johnson [9] insofar as they

observed dilatation of the right ventricle and right auricle and a contracted state of the left ventricle. There seems to be no doubt that the left ventricle is in a condition of greater tone and smaller volume than the right and that its output of blood per unit of time is less than that of the right ventricle. The left auricle is moderately dilated. We may, therefore, assume that there is less diastolic filling of the left ventricle, its increased tonus being related to the markedly elevated systemic arterial pressure. It was also frequently observed that the right side of the heart contracted periodically, when all movement of the left ventricle had ceased, in animals autopsied three to five minutes after injection of adrenalin.

We were, however, unable to confirm the assumption of Auer and Gates[8] and of Loeb[11] that a pathologically elevated negative pressure was responsible for the occurrence of pulmonary edema. Our measurements showed a smaller *range* of intrapleural pressure, with the mean point between the inspiratory and expiratory intrapleural pressure approximately the same as that present before injection of adrenalin. We believe, therefore, that Welch's fundamental postulate of the cause of pulmonary edema applies to the condition that obtains in rabbits after intravenous injection of adrenalin, namely that there is an inequality in the output of the two ventricles, the right ventricle discharging an increased volume of blood into the lungs, the left ventricle emptying a smaller volume of blood into the systemic arterial system. The fact that the venous pressure is so little elevated under these circumstances confirms the interpretation that the right ventricle is emptying all the blood supplied to it.

In the presence of an increased discharge of blood from the right ventricle and a decreased output from the left, blood accumulates in the capillaries of the lung under increased pressure. This causes the diapedesis of red blood cells which may be observed within one minute after injection of adrenalin. In one-half to one minute later, a serous exudate filters through the capillary wall into the alveolar spaces. Our evidence suggests, to our mind, that the high capillary blood pressure is the significant factor in the pathogenesis of pulmonary edema due to adrenalin. It would seem likely that acute pulmonary edema when it occurs in human subjects as a result of left ventricular failure can be explained by a mechanism similar to the one which we have outlined.

The explanation of the therapeutic effect of positive pressure respiration appears to be more complicated. Although it has been shown in the roentgen-ray studies reported in this paper that dilatation of the right heart could be prevented, as well as pulmonary congestion and edema, by positive pressure respiration, we are not able to conclude that a decreased entrance of blood into the right heart is the sole or even most important factor. Edema of the lungs may be prevented by a degree of positive pressure which only slightly decreases the size of the heart. Furthermore, the application of even moderate positive pressure decreases significantly the mean intrapleural negative pressure. During continuous positive pressure respiration

the intrapleural pressure at the end of expiration is slightly above that of the atmosphere; during intermittent inflation of the lung, the intrapleural pressure during the inspiratory (or distending) cycle of respiration is also slightly above that of the atmosphere. We are, therefore, forced to conclude that the increase in positive pressure within the chest exerts an opposing force tending to hinder the outpouring of both red corpuscles and serum from the pulmonary capillaries. Although anoxemia is undoubtedly present as a result of the extreme shallowness of respiration, and although this is known to increase capillary permeability, the swiftness of development of the condition and the rapidity with which it may be stopped argues against anoxemia as a major influence.

Our experiments therefore lead to the conclusion that both the factors which we have just discussed operate to prevent or stop pulmonary edema. (1) A diminished volume of blood entering the right heart and hence the lung, due to the increased positive pressure within the chest. This in itself would result in a lower capillary blood pressure and, therefore, a decreased tendency for red corpuscles and serum to pass through the capillary wall. It may also be true that an intermittent application of positive pressure might squeeze some additional blood into the left auricle and into the ventricle, with an increased output of blood into the systemic arterial system. Since our studies showed no elevation of systolic arterial pressure under these conditions, we have no evidence to support this hypothesis. (2) The increased positive pressure shown to exist within the chest as a result of positive pressure respiration exerts an opposing force against the capillary wall which physically retards the outward filtration of red cells and serum. (3) Anoxemia is an additional although probably less important factor which increases capillary permeability. Distention of the pulmonary capillaries may also play a part in augmenting capillary permeability.

3. Physiological Measurement of the Effect of Positive Pressure on Human Subjects

The physiological effects of positive pressure respiration were studied in normal subjects, patients with congestive heart failure, and in a miscellaneous group. The measurements chosen were the pulse rate, respiratory rate, blood pressure, venous pressure, circulation time and vital capacity. The pressure varied from 3 to 8 cm. of water, administered continuously by means of a rebreathing apparatus consisting of a motor blower unit, a control valve inserted in the respiratory tubing, a water manometer and a soda lime container. The patient was connected to the apparatus by means of a mouthpiece, a mask or a hood with closure at the neck. This has been described elsewhere in detail in connection with helium-oxygen treatment.[26] In some cases a basal metabolism apparatus was used with a weight on the bell to give the required pressure.

Data on Normal Subjects

Ten normal subjects were tested. They breathed oxygen for a control period of five minutes under atmospheric pressure, oxygen under 3 cm. water pressure for five minutes, oxygen under 6 cm. water pressure for five minutes and oxygen under atmospheric pressure as the final control period.

The *pulse rate* in two of the ten cases showed no change when breathing oxygen under 6 cm. pressure. In eight cases, there was a decrease in rate, averaging 7 beats per minute. The *respiratory rate* was slightly increased in two subjects, decreased in three, with no change occurring in the remaining five. No significance can be attached to variations in respiratory rate in these tests. The *systolic and diastolic arterial pressure* also showed no appreciable alteration in the ten tested subjects.

However, the effect of positive pressure on the *venous pressure* was to cause a consistent slight elevation in the majority of instances; thus in eight of the ten individuals breathing against 3 cm. of pressure there was an average rise of 10 millimeters of water and in nine subjects breathing against 6 cm. of pressure there was an average rise of 20 mm. of water (table 1).

Table I

Effect of Positive Pressure Respiration on Venous Pressure in Normal Subjects

Subject No.	Oxygen Under 0 cm. Pressure	Oxygen Under 3 cm. Pressure	Oxygen Under 6 cm. Pressure	Oxygen Under 0 cm. Pressure
1	62	72	88	48
2	52	50	75	42
3	40	54	63	44
4	53	65	76	58
5	160	151	157	
6	67	77	88	60
7	77	83	93	78
8	103	122	125	108
9	68	73	85	70
10	93	101	107	92

The interpretation of this finding appears to be that the increased pressure within the chest produces a resistance to the entrance of blood in the right heart, thus creating a measurable elevation of the pressure in the systemic venous system. This explanation is further confirmed by the results on the *circulation time,* which show in the majority of instances a slight although definite prolongation. Thus, in five of nine subjects there was an average prolongation of circulation time of 3.3 seconds when the subjects breathed against 3 cm. of water pressure, and in six out of nine subjects a prolongation of 3.6 seconds when the subjects breathed against 6 cm. of water pressure (table 2). The effect of positive pressure, therefore, appears to be a slowing of the velocity of blood flow through the lung (arm to tongue time). From the results on the circulation time and the venous pressure it seems likely that the heart deals with a smaller volume of blood under these circumstances, presumably with a slower total blood flow.

TABLE II

Effect of Positive Pressure Respiration on Circulation Time in Normal Subjects

Subject No.	Oxygen Under 0 cm. Pressure	Oxygen Under 3 cm. Pressure	Oxygen Under 6 cm. Pressure
1*	26.0*	9.0*	23.0*
2	19.0	17.8	16.7
3	22.6	26.0	22.8
4	16.4	19.0	20.0
5	20.4	19.8	21.2
6	18.8	18.0	24.2
7	18.2	21.4	22.6
8	19.2	22.6	23.8
9	16.2	20.2	18.5
10	16.0	13.8	17.6

* Taken with saccharin (excluded); other tests done with sodium decholin.

The *vital capacity* in nine out of ten subjects showed an average decrease of 350 c.c., which may perhaps be accounted for by the fact that there is already an increase in the volume of air in the lungs as the result of positive pressure of approximately 300 to 400 c.c. when the vital capacity deter-

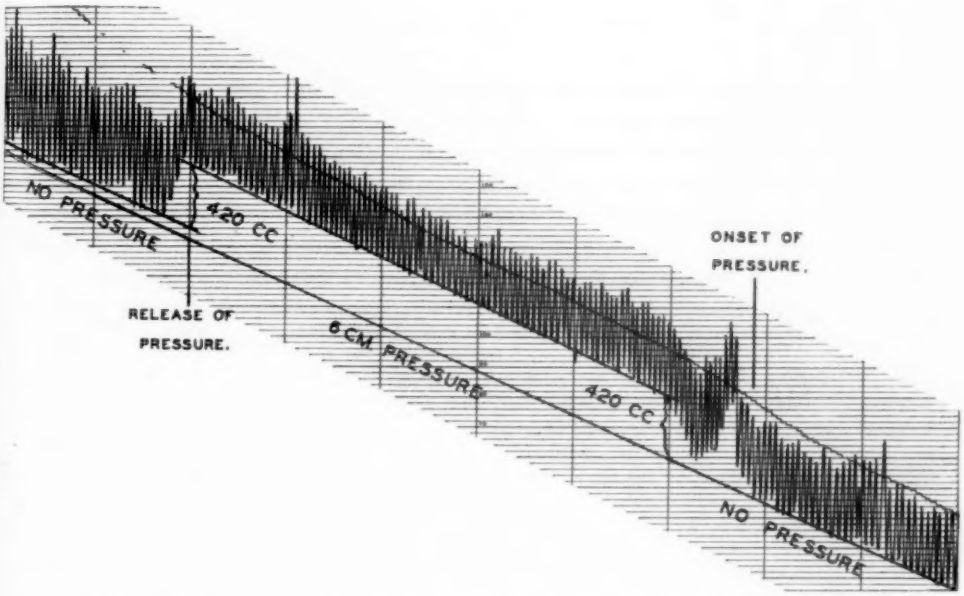


CHART 7. Effect of positive pressure respiration on the volume of gas in the lungs.

mination is made. In the accompanying graphic record of the effect of positive pressure respiration on the volume of gas in the lung (chart 7), it will be observed that a normal individual at the onset of pressure took into his lungs an additional 420 c.c. of oxygen; when the pressure was released, this additional volume of gas left the lung.

Effects of Positive Pressure Respiration in Patients with Congestive Heart Failure

Fourteen patients with congestive heart failure were tested as to their response under positive pressure. The degree of passive systemic venous congestion (i.e. congestive failure) may be seen from the control venous pressure measurements. The patients were divided into two groups of seven each.* In the first, control observations were taken while the patient was breathing air and oxygen for 5 minute periods at atmospheric pressure. The patients were then switched to breathing oxygen at 8 cm. water pressure for an 8 minute period and observations taken at the end of this time. Additional observations were recorded 3 minutes after pressure was withdrawn, while the patient was breathing air. In the second group, the patients breathed air during the control period, air during the administration of positive pressure (which in this group was 6 cm. of water) and 3 minutes after pressure was withdrawn. The results may be summarized as follows: The *pulse rate* during positive pressure breathing was increased in six cases, averaging 6 beats per minute; decreased in one case, and no change in one case. In the group exposed to 6 cm. positive pressure, the pulse rate was increased in two cases, decreased in three, and no change in two cases. No significance could be ascribed to these changes, psychic influences and perhaps fatigue in all probability overshadowing the physiological influence of positive pressure. The same interpretation can be ascribed to the results on *blood pressure* in both groups. Excluding changes under 8 mm. Hg there were only three instances in both groups in which a marked change was observed. In these cases the systolic blood pressure rose 52 mm. in one case, 30 mm. in the second, and 25 mm. in the third. The diastolic blood pressure rose 38 mm. in the first case, 11 mm. in the second case and 18 mm. in the third case. In the remaining 12 cases the variations were negligible.

The *respiratory rate* in the first group was decreased in five cases an average of 3 breaths a minute, and increased in two, an average of 8 breaths per minute. In the second group exposed to 6 cm. positive pressure the respiratory rate was decreased in all, averaging 9 breaths per minute. The characteristic response to the inhalation under positive pressure is a decrease in the rate of respiration, although it did not occur in all of our cases.

As in the controls, the most consistent changes were in the *venous pressures.* In the group exposed to 8 cm. positive pressure, there was an elevation of venous pressure in seven instances, averaging 43 mm. of water, with a decrease in only one. In the group exposed to 6 cm. water pressure, there was an elevation of venous pressure in six instances, averaging 28 mm. of water, with a decrease in one (table 3). The degree of elevation of venous pressure in the patients with congestive heart failure was greater than in the control subjects who averaged an increase of 20 mm. of water when exposed to 6 cm. of pressure.

* In the first group of seven patients a repeat observation is made on one case, no. 4, so that the data will be presented as if there were eight cases instead of seven.

TABLE III

Effect of Positive Pressure Respiration on Venous Pressure in Patients with Congestive Heart Failure

Case No.	Before Application of Pressure		After Application of Pressure	
	Breathing Air	Breathing Oxygen	Breathing Under Pressure Cases 1–7 Oxygen Cases 10–16 Air	5 Minutes After Pressure Was Withdrawn Breathing Air
1	206	184	225	172
2	100	90	190	105
3	65	82	120	65
4	15	15	25	8
4A	5	−8	25	2
5	105	105	90	80
6	74	78	94	73
7	105	93	155	
10	207		230	200
11	88		109	105
12	125		140	100
13	80		120	78
14	180		160	170
15	135		175	165
16	40		70	40

The effect of positive pressure on the *circulation time* was less consistent, perhaps due to the fact that many of these patients were too ill to furnish complete coöperation. Some of them had difficulty in keeping the mouthpiece in place during the entire period and the circulation time was taken within 3 minutes after pressure was withdrawn in these cases. The results may be summarized as follows: In the group exposed to 8 cm. positive pressure the circulation time while the patient was on the apparatus was unchanged in two. In two others it was markedly increased, one of them showing a prolongation of 16.5 seconds and the other 10.0 seconds. In the group exposed to 6 cm. positive pressure, observations were taken within 3 minutes after pressure was withdrawn. In two cases there was no change, but in three others there was a marked prolongation, averaging 17 seconds. Although lengthening of the circulation time did not occur in all instances, the change when it did take place was much more marked than in the control subjects in whom prolongation of the circulation time when breathing against 6 cm. positive pressure averaged only 3.6 seconds (table 4).

The *vital capacity* showed no consistent changes in the group breathing under 8 cm. positive pressure. However, in the group breathing under 6 cm. positive pressure, approximately 5 minutes after conclusion of the test, there was a rise in six out of seven patients, averaging 216 c.c. The fact that this rise in vital capacity did not occur in the group breathing under 8 cm. positive pressure may be accounted for perhaps by the greater fatigue induced in the latter group by a longer experiment. A possible explanation

for the elevation in vital capacity is that some blood was forced out of the lungs into the left heart during the test, allowing greater lung space, although this must be presented only as a tentative hypothesis.

TABLE IV

Effect of Positive Pressure Respiration on Circulation Time in Patients with Congestive Heart Failure

Case No.	Before Application of Pressure		After Application of Pressure	
	Breathing Air	Breathing Oxygen	Breathing Oxygen Under Pressure	3 Minutes After Pressure Was Withdrawn Breathing Air
1	43.6			53.1
2	45.0		61.5	
3	14.0		14.0	
4	40.0		38.2	32.0
4A	39.0			40.5
5	31.0		41.0	
6	24.0			25.0
7	16.5			24.5
10	32.0			65.0
11	43.0			47.0
12	43.0			44.0
13	54.0			54.0
14	18.0			33.0
15	37.0			
16	23.0			

We wish to present three charts showing the significant changes in typical experiments. In the chart below (chart 8) the effect of breathing against positive pressure is shown in a patient with congestive heart failure. It will be seen that the venous pressure declines during the control period from 205 to 182 mm., begins to rise after the application of 3 cm. positive pressure, shows a still more marked elevation at 6 cm. positive pressure, reaching 225 mm., and then falls abruptly when the pressure is removed. The circulation time rose from 43 seconds to 53 seconds.

In a patient with asthma (chart 9) the venous pressure rose only slightly with 3 cm. positive pressure, from 30 to 40 mm., but rose to a height of 75 mm. when 6 cm. positive pressure was used, falling to 25 mm. when pressure was withdrawn. No significant changes took place in blood pressure or pulse or respiratory rate in any of these cases.

The last chart represents a reaction in a patient with neurocirculatory asthenia (disordered action of the heart) to positive pressure respiration (chart 10). The patient, a young man of 22 years, came to the hospital complaining of breathlessness at rest, palpitation and continuous heart consciousness. He was extremely apprehensive. On examination, his heart showed no abnormalities, the electrocardiogram was normal and roentgen-ray of the heart revealed no enlargement. The test was performed with the

patient in a helmet, a leak-tight closure being made at the neck. Oxygen was breathed throughout. The chart shows that when he was breathing against 2 cm. positive pressure, there was a distinct rise in venous pressure

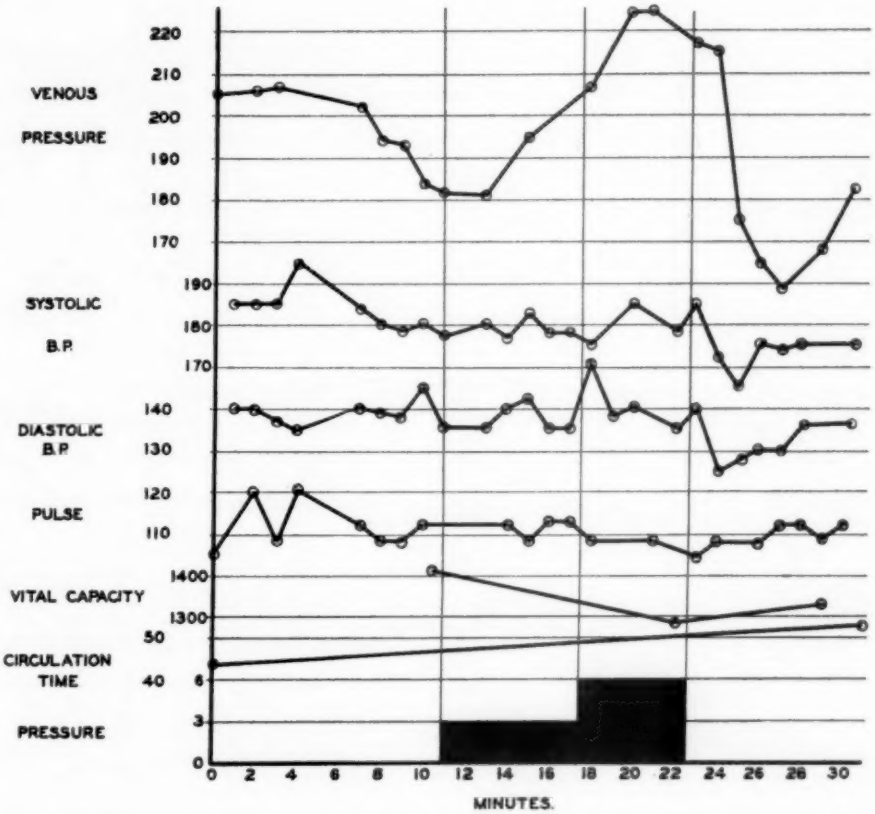


CHART 8. Effect of breathing against positive pressure in a patient with congestive heart failure.

on two occasions, from 90 to 120 mm. When the pressure was raised to 5 cm., the venous pressure rose still further to 138 mm. and dropped abruptly to 90 when the pressure was removed. The circulation time increased from 18 seconds to 27 seconds while he was breathing under 5 cm. water pressure.

This case is of considerable interest in that it portrays physiological changes in a patient whose circulatory symptoms are of nervous origin. In another patient who had anxiety neurosis but without symptoms referable to her heart, the same test showed no elevation of venous pressure when breathing against 2 cm. water pressure and no change in circulation time. It would seem likely, therefore, that the rise in venous pressure which occurs after breathing against positive pressure is an indication of an inability of the heart to compensate for an arbitrarily induced back pressure by an increased blood flow. In normal individuals a mechanism exists whereby

the circulation time is only slightly affected by resistance to the flow of blood into the heart, whereas in patients with heart disease, especially congestive failure, marked retardation of the velocity of blood flow may take place.

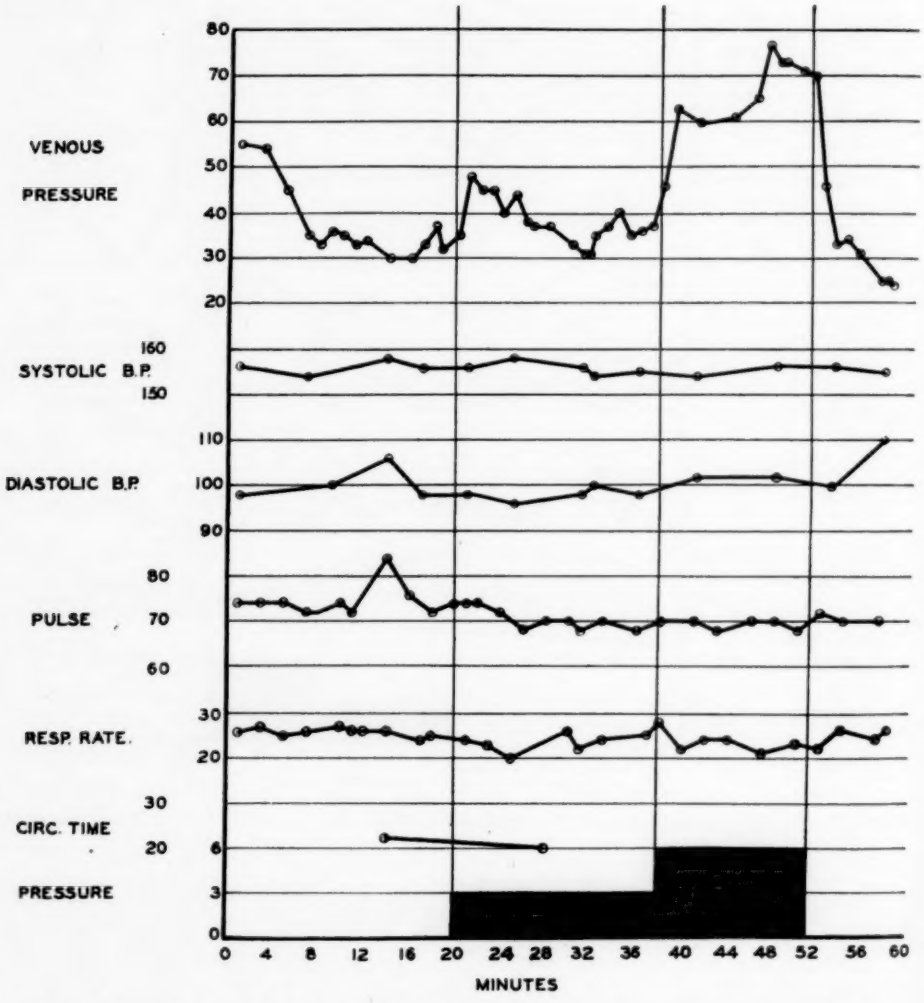


CHART 9. Effect of breathing against positive pressure in a patient with asthma.

An explanation of the relatively marked increase in venous pressure and prolongation of circulation time in patients with congestive heart failure exposed to positive pressure respiration invites consideration of several influences. In the first place, the increase of positive pressure within the chest interposes an obvious difficulty to blood entering the right auricle. However, this physical difficulty would appear to be of similar magnitude, other factors being equal, in normal subjects who, however, show comparatively

slight changes. It has recently been shown by Christie and Meakins [27] that the patient with congestive heart failure has an intrapleural pressure range that is more nearly atmospheric than the normal individual, especially during expiration. The presence of so much additional blood in the lungs inter-

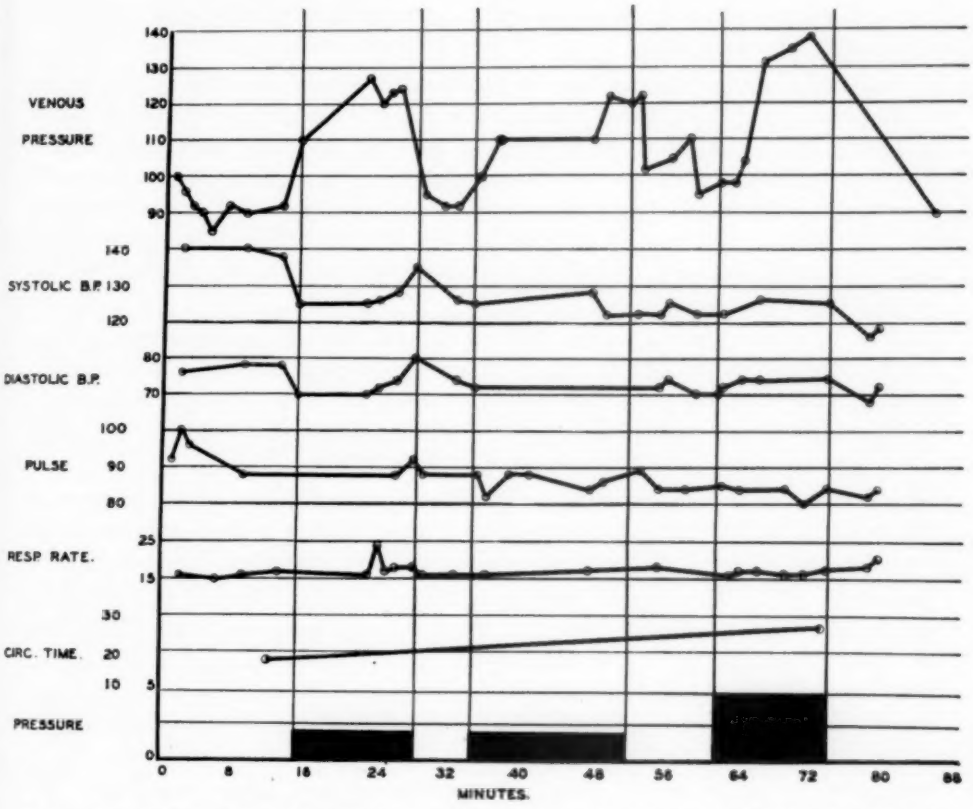


CHART 10. Effect of breathing against positive pressure in a patient with disordered heart action.

feres with the elasticity of the pulmonary membrane with the result that the cardiac patient is unable to achieve as high a negative pressure during the inspiratory cycle as the normal person. The cardiac patient would therefore be less able to increase the negative pressure within the chest and so in part lessen the additional positive pressure imposed on the lung from without, whereas the normal individual by an increase in the velocity and depth of breathing could increase the negative pressure within the chest to a degree which would practically overcome the arbitrarily imposed external positive pressure. In this way an explanation is afforded of the relatively small increase in venous pressure and the relatively insignificant interference with the velocity of the circulation that normal individuals show. Some of the variability in our results in patients may also perhaps be explained in

this way, since an individual who because of psychic influences was hyperventilating at the time the circulation test was being made might be temporarily developing an increase in the negative intrapleural pressure which would augment the blood flow. As pointed out in the historical section of this paper, it has been repeatedly shown that an increase in the negative pressure within the chest increases the blood flow both through the lungs and the peripheral circulation.

An additional influence may be set forth, namely, that the presence of an increased positive pressure within the chest interferes with the diastolic filling of the ventricles and the auricles as well, and that this interference would be more apt to have an adverse influence in a diseased heart muscle than in a normal one. It also seems likely that the increased pressure within the lung may in the case of an insufficient right ventricle retard a complete emptying of that chamber of the heart, thus causing a further back pressure of blood into the systemic veins.

We have not discussed up to the present whether this repression of blood into the systemic venous reservoir is an adverse or a beneficial influence. At first sight it might seem that such a slowing of the circulation time would but increase the congestion of the viscera and extremities and thereby accentuate the harmful effects of heart failure. We must consider, however, that this effect is accomplished by decreasing the volume of blood passing through the heart. The heart is at this time dealing with a smaller blood volume which would decrease the burden upon it, and thus have a beneficial influence. One has only to remember the dramatic improvement in some cases with acute congestive heart failure particularly in left ventricular failure that is engineered by withdrawal of 500 c.c. of blood. Striking improvement in the circulation has also been reported by tourniquets applied to the lower extremities. In both instances, the heart muscle for a brief period of several hours is allowed to function on a smaller volume of blood and its recuperative power under these circumstances is at times startling. We feel justified in broaching the proposition that positive pressure respiration, properly controlled, may diminish the volume of blood the heart has to deal with and, therefore, constitute a beneficial rather than an adverse influence. Studies with this in mind are contemplated, namely, the effect of more continuous but somewhat milder degrees of positive pressure administered continuously during inspiration and expiration to patients with various forms of heart failure. We have outlined the discussion at this time, since it may account in part for some of the improvement observed in treating patients with pulmonary edema, to be described in the following section.

The Clinical Use of Positive Pressure Respiration in Acute Pulmonary Edema

The technic of applying positive pressure continuously throughout the respiratory cycle has been described in detail in connection with helium-

oxygen therapy.[26, 30] The method consists of the provision of a closed circuit apparatus in which the ventilation and pressure are achieved by a motor blower unit capable of maintaining a pressure as high as 10 cm. of water. In the earlier cases, a mouthpiece or mask was used to connect the patient with the apparatus. Later a hood was employed which made closure at the neck, modelled after the Benedict helmet metabolism apparatus. We shall present eight case histories which illustrate the clinical use of this therapeutic procedure.

Case Reports

Case 1. A female, aged 54 years, had suffered from nervousness, weakness and heart pounding for four and a half years; on examination she was found to have a toxic adenoma. The basal metabolic rate was plus 27 per cent. The heart was moderately enlarged, blood pressure 200 systolic and 100 diastolic. The heart rate was 140. After iodine administration and rest in bed, she improved and thyroidectomy was performed. The day after operation she showed signs of advanced cardio-respiratory failure and became intensely dyspneic and cyanotic. Supra-sternal retraction was evident during inspiration. The pulse rate was rapid, 140, thready volume and soft. Blood pressure dropped to 80 systolic and 60 diastolic and returned to 120 systolic and 80 diastolic. The venous pressure climbed to 280 mm. Moist râles were heard throughout both lungs and audible gurgling appeared in her throat. Her head moved backward with each inspiration. Respiration was extremely shallow and rapid, rate 50. She appeared moribund.

She was treated with inhalation of 50 per cent helium and 50 per cent oxygen under a pressure of 7 cm. of water, lowered later to 5 cm. Within 15 minutes, the signs of pulmonary edema had disappeared. There were no gurgling noises, the moist râles were no longer audible. Improvement continued. She became conscious and five hours later breathing was deep and easy, the lungs were clear, cyanosis was greatly lessened. The pulse was of good volume, rate 120, blood pressure 160 systolic and 120 diastolic. Venous pressure was 125 mm.

The patient's temperature, however, continued to rise. When the mouthpiece rebreathing apparatus was removed for one minute, the signs of edema began to reappear. During the night she showed returning circulatory failure, pulse rate 160, venous pressure 250 mm., blood pressure 190 systolic and 100 diastolic, dropping later to 130/?. Temperature was 107° F. She died the following morning. Before death, no râles could be heard over the front of her chest.

A thyroid crisis associated with circulatory failure was the apparent cause of death. The earlier clinical improvement as a result of the application of positive pressure was striking. Helium was added to oxygen because the marked suprasternal retraction suggested some degree of obstruction of the respiratory passages. The rapid disappearance of edema was distinctly due to the administration of pressure, as it recurred almost immediately after withdrawal of positive pressure. The cause of edema seemed to be mainly the result of left ventricular failure.

Case 2. A male, aged 50 years, developed acute bronchopneumonia following hemorrhage from a tuberculous lesion. On the fourth day, acute pulmonary edema, together with signs of cardiac failure, was manifest. The pulse became rapid, 150, thin and thready, and the liver was palpable two fingers below the costal margin. A mixture of 50 per cent helium and 50 per cent oxygen was given under 5 cm. pressure. Physical examination of his chest one hour later revealed absence of all moisture in the lungs. Twelve hours later, the pulse was 100, respiratory rate was 24, and he was comfortable. The rebreathing pressure apparatus was removed without recurrence of edema. However, the patient's temperature rose abruptly with

a spread of the bronchopneumonic process, but without pulmonary edema. He died 24 hours later.

The cause of pulmonary edema was thought to be due to the joint influence of left ventricular failure and increase in capillary permeability associated with inflammation of the lung and anoxemia.

Case 3. Male, aged 62 years. History: The patient's mother had asthma and he himself suffered from hay fever for six years. Asthma began three years before admission, relieved by adrenalin. Patient entered the hospital in a state of severe status asthmaticus unrelieved by three injections of adrenalin, 1 c.c. each, and an injection of morphine, gr. ¼ during a five hour period. He was in a generalized spastic state with marked carpopedal spasm. Inspiratory dyspnea was extremely severe and the patient suddenly stopped breathing. After injection of 1 c.c. of adrenalin he began breathing again but with extreme difficulty. The respiratory rate decreased progressively to two per minute. Blood pressure dropped from 170 systolic and 110 diastolic to 110 systolic and 70 diastolic. He developed edema of the lungs and frothy fluid came into his mouth. He was pale, eyes were rolled back and his jaws clamped. The pupils did not react to light. Inspiration was short, respiration prolonged with a high-pitched sibilant whistle. The pulse was at first fast and irregular and later imperceptible. Fifty c.c. of 50 per cent glucose intravenously had been administered without noticeable effect. He was then put in the hood helium apparatus with 21 per cent oxygen and 79 per cent helium and 5 cm. water pressure. Breathing increased in depth and rate and the pulse became palpable. He was given 10 c.c. of calcium gluconate and 20 c.c. of dilute hydrochloric acid (1–1,000) intravenously without effect on the marked spasm. Metrazol was injected subcutaneously in 4 c.c. doses at two hour intervals for three doses. The breathing progressively improved and 12 hours later he was out of danger with slight asthma persisting. The signs of edema disappeared within the first hour of the treatment. On the following day helium was discontinued and the day after the patient was free from asthma. He left the hospital without asthma, one week later.

In this patient edema of the lungs appeared to develop as a result of:

1. A previously existing pathologically elevated negative pressure due to inspiratory dyspnea, which exerted a suction action on the pulmonary capillaries.
2. Fatigue and imminent paralysis of the respiratory center. (To be discussed in case 7.)
3. Left ventricular failure.

The rapid pulse with marked decrease in volume which patients with asthma develop appears to be due to the high negative pressure existing within the chest which facilitates the entrance of blood into the right side of the heart and into the lungs but retards the passage of blood from the chest into the aorta. It may be generally observed that the volume of the pulse is either markedly diminished or becomes imperceptible at the end of the inspiratory cycle when the negative pressure within the chest is at its height. During expiration the pulse returns and increases in volume. The blood pressure frequently drops below the point of determination at the end of inspiration. It seems, therefore, likely that in this patient passive pulmonary congestion was present due to the failure of the left ventricle to discharge the customary volume of blood.

Case 4. A female, aged 37 years, became acutely ill two days after onset of a coryza, with the development two days later of signs of consolidation in the right upper lobe. She showed progressive pulmonary involvement, with high fever and marked toxicity. All lobes showed consolidation except the left lower lobe. The sputum and blood contained pneumococcus type V. Treatment with positive pressure, 5 to 7 cm. water, and 100 per cent oxygen was applied when exitus seemed

momentarily imminent. She was comatose and deeply cyanotic. Respiration was very labored with moist râles heard extensively over the anterior portion of the chest and in the throat. Retraction was present in the supraclavicular fossa. Pulse was very thin, rate 150. Blood pressure had dropped from 160 systolic and 85 diastolic to 110 systolic and 50 diastolic.

Within 15 minutes after initiation of positive pressure, all signs of edema cleared. She breathed more deeply, with less supra-sternal retraction and labor. Cyanosis was markedly diminished and pulse rate and volume improved. No decline in fever or toxicity occurred, and she died 48 hours later, temperature 106.2°. The signs of edema continued to be absent as long as positive pressure was maintained, but returned when the apparatus was removed. The cause of the pulmonary edema was thought to be increased capillary permeability due to inflammation and anoxemia, with left ventricular failure as a contributory cause.

Case 5. A male, 72 years, showed a rising temperature the day after a second stage supra-pubic prostatectomy. On the fourth day his temperature was 104.6°, pulse 120, thin and soft, respirations 40. He became comatose, moist râles appeared throughout the lungs, and he appeared moribund. The clinical diagnosis was bronchopneumonia, edema of the lungs, cardiac insufficiency. He was treated with 100 per cent oxygen under a pressure of 5 cm. of water, using a mouthpiece rebreathing apparatus. The signs of edema were markedly decreased within 15 minutes, the pulse rate decreased from 120 to 108, his breathing was deeper, and moderate cyanosis previously present was much lessened. His lungs did not again show outspoken edema. However, his pulse weakened and on the following morning, 20 hours after the onset of positive pressure, he died, death being due to cardiac failure. The cause of pulmonary edema was thought to be left ventricular failure with an increased capillary permeability due to pneumonia.

Case 6. Female, aged 26 years. History: The patient had pneumonia two months previously. She now entered the hospital with fever, dyspnea and a pain in her chest for four days. A rising temperature and pulse continued for three days and she appeared extremely ill with severe dyspnea accompanied by neck muscle retraction on inspiration and a moderate degree of cyanosis in an oxygen tent with 50 per cent oxygen concentration. The respiratory rate was 40. Examination of the lungs revealed fine crackling (crepitant) râles over the right upper lung and the left upper lung and left axilla, with many moist râles over the anterior and axillary regions on the left side. Over the heart presystolic and systolic murmurs were heard at the apex. The pulse was 120 and small in volume. White blood cells 20,600, polynuclears 86 per cent. Sputum culture revealed Friedländer's bacillus.

The patient was treated with 100 per cent oxygen under a positive pressure of 3 cm. of water. After 15 minutes there appeared to be a definite although not marked diminution in the number of moist râles over the left anterior chest. However, there was no change in the number or character of the fine sticky râles. One hour later there seemed to be a slight further lessening of the number of moist râles. On the following day the patient was improved. There was a smaller number of both fine and medium moist râles over the chest. She was treated for one hour with 100 per cent oxygen under a positive pressure varying from 3 to 5 cm. of water. There was no definite change in the râles in the chest. The patient appeared completely comfortable in the hood on both occasions. The dyspnea was less marked and there was a distinct lessening of the retraction of the neck muscles during inspiration.

No consistent changes were observed in either the systolic or diastolic blood pressure, the pulse and respiratory rates. No change in the venous pressure could be attributed to breathing against 3 cm. positive pressure but when 5 cm. was employed there was a consistent but very slight increase of the venous pressure, ap-

proximately 10 mm. of water. This degree of elevation of the venous pressure is extremely little when compared to the effect of positive respiration on patients with congestive heart failure, and indicates that the patient was able to compensate in some way for the resistance interposed to the flow of blood into the right heart. In fact, normal subjects generally showed a rise of 20 mm. of water; this may be due to the increased blood flow associated with the pneumonia.

The patient gradually improved and recovered. The case is presented primarily to indicate that positive pressure respiration of the degree employed does not result in a disappearance of râles which are presumably of an inflammatory etiology. There was no change in the fine sticky râles although there was a slight but definite diminution of the larger moist râles over the front of the left chest. The function of positive pressure in causing a more marked relief of dyspnea was clearly revealed. The inspiratory neck muscle retraction gave evidence that the widely consolidated lung was moved only by a markedly increased inspiratory effort. This was plainly alleviated by the inhalation of oxygen under positive pressure. It was also of interest that no significant changes occurred in the circulation except the extremely slight elevation in venous pressure noted above. Although the large and medium-sized moist râles appeared to indicate the beginning of pulmonary edema it is impossible to state that the short period of treatment given the patient had anything to do with the outcome. The case is presented not as a therapeutic result but to indicate the limitations of positive pressure respiration in checking or in removing inflammatory exudate, in the same time interval in which a transudate of edema fluid can be abolished. It is not possible to say what a longer period of treatment would have accomplished but it is of interest that the patient was more comfortable under positive pressure respiration than she was in atmospheric oxygen.

Case 7. Male, aged 59 years. History: Following an attack of bronchopneumonia, which seemed to clear, the patient developed asthmatic breathing, a harassing cough, and mucopurulent expectoration. The asthmatic breathing, though varying in intensity, became progressively worse in the succeeding two months, and was unrelieved by adrenalin, rest in bed, or oxygen. There were apparently no contributory factors in the past history. He was removed to the hospital in acute distress, breathing with severe difficulty, with markedly prolonged expiration. Sibilant râles were heard throughout the chest. Moderate relief was obtained by two treatments of helium and oxygen under 4 cm. positive pressure. He was put into an oxygen tent, oxygen concentration 50 per cent, for the night with the idea of resuming helium therapy in the morning. Three doses of morphine, grains ¼ each, were given during the night, the last administered without the knowledge of the attending physician. When he was seen in the morning his condition appeared moribund. He was a large well-developed man, cyanotic even in 50 per cent oxygen. Respiratory rate had declined to 2 to 4 times a minute. The breathing took place as a short gasp, accompanied by a loud mucous gurgling which emanated from his throat and partially obscured the moist and sibilant râles heard on auscultation over the front of the chest. His pulse was full and bounding, rate 90, apparently an asphyxial pulse. He had been given 50 c.c. of 50 per cent glucose intravenously without noticeable relief. In the presence of what appeared to be imminent asphyxia due to respiratory failure he was given 21 per cent oxygen and 79 per cent helium under 5 cm. positive pressure, at first through a mouthpiece and later through a mask closed-circuit apparatus. Within 10 minutes signs of pulmonary edema had cleared and auscultation of the chest showed that both lungs were being ventilated, accompanied by sibilant râles in inspiration and expiration. The respiratory rate had increased to 16. He was given 4 c.c. of metrazol and 20 grains of caffeine sodium benzoate in divided doses during the first half hour. The patient progressively improved and in an hour and a half opened his eyes and was partly conscious. His pulse was rapid, rate 136, but of

fair quality. He was kept on the helium-oxygen mixture for three days, the pressure being gradually lowered from 5 to 2 cm. of water. At the end of that time the patient was in generally good condition. Although a moderate amount of asthmatic breathing continued, his pulse declined to 86 and he was eating three good meals a day.

On two subsequent occasions the patient developed severe obstructive dyspnea which required helium treatment for a period of a week almost continuously, with intermittent inhalations of helium with oxygen at intervals following the continuous treatment. He was treated with autogenous and stock vaccines, potassium iodide and roentgen-ray therapy. Two bronchoscopies were performed which revealed unusually small bronchi, their diameter comparable to that expected in an older child. After a series of reversals the patient seemed on the road to recovery, although at no time was his chest free from sibilant râles. For a period of one month, however, he seemed in such good condition as to be allowed up in a chair and to do a small amount of walking. A graphic record of his tidal air showed expiration to occupy 69.9 per cent of the respiratory cycle, whereas three months before it was 86.7 per cent. It is noteworthy that at no time did injection of adrenalin clear the râles in his chest, although improvement was often noted following its use, and some improvement following the inhalation of a 1–100 adrenalin spray. The patient had planned to leave the hospital in one week, when a return of severe difficult breathing took place, apparently associated with increased activity. His condition became progressively worse, and finally gasping respiration necessitated the use of helium and oxygen with a positive pressure of 5 cm. of water. This gave him a moderate degree of relief, and it was thought that the condition would yield to treatment as it had three times in the past. However, each time the hood was removed, the patient was plunged into severe uncontrollable obstructive dyspnea. The patient died one week later of respiratory failure.

The diagnosis of this patient was (1) obliterative bronchitis and bronchiolitis of infectious origin, (2) edema of the lungs (the morning after admission to the hospital).

There was evidently not only an unusual narrowing of the main bronchi, but also a progressive intimal thickening of the bronchioles as well. The patient was in the hospital six months. It was believed that in the next to the last week of illness helium-oxygen therapy was postponed for a period sufficient to cause a marked increase in edema of the walls of the smaller bronchi and bronchioles due to the persisting pathologically elevated negative pressure within the chest.

The patient's reaction to helium-oxygen treatment under 5 cm. water pressure the morning after admission could be attributed mainly to the maintenance of the positive pressure, which appeared to result in a swift disappearance of pulmonary edema, the restoration of pulmonary reflexes and return of activity of the respiratory center. The function of helium was undoubtedly to allow a deeper penetration of the mixture of 21 per cent oxygen and 79 per cent helium, but this could not have been achieved unless the edema had first cleared.

The cause of the initial pulmonary edema was considered due to (1) the previous presence of a high intrathoracic negative pressure resulting from inspiratory dyspnea, (2) the administration of excessive doses of morphine. By depressing the respiratory center, the respiratory rate was not only markedly decreased but there was a diminution in expiratory effort. The patient with asthma, by maintaining a prolonged expiration against a constricted orifice, develops an increased positive pressure between the site of obstruction and the alveolar capillaries. The abrupt termination of this pressure, by decreasing the intensity and rate of respiration, is followed by an increase in permeability of the capillary wall, as will be more fully discussed later.

Case 8. Male, aged 50 years. History: Patient entered hospital complaining of

epigastric distress, an aching pain in the lower left chest of six months' duration. He had a productive cough with blood streaked sputum and during this period lost 22 pounds. When he was admitted to the hospital, examination of the chest showed bronchial breathing and dullness over the left lower lobe. The brachial arteries were palpable, blood pressure was 130 systolic and 75 diastolic. As a result of bronchoscopy and biopsy, a diagnosis of carcinoma of the left bronchus with involvement of the lung, atelectasis and pleural effusion was made. Following a finger infection, for which he was given prontylin, he developed bronchopneumonia on the ward with widespread consolidation, and, two days later, edema of the lungs. He became deeply cyanotic, a loud gurgling was heard in his throat and moist râles over the chest. His pulse was 136 and of small volume, respiratory rate 40, temperature 103°. The administration of 50 per cent oxygen in an oxygen tent only slightly relieved the marked cyanosis. Positive pressure respiration was used with 100 per cent oxygen under 6 cm. water pressure and within one hour the patient was much improved, there was no gurgling to be heard in the throat and many but not all of the moist râles had cleared. His color was markedly improved. A roentgen-ray of the chest showed a tremendous amount of irregular consolidation and metastases as well as marked cardiac enlargement. One hour after positive pressure respiration, a repeat roentgen-ray of the chest at the same distance showed the heart shadow was decreased 1.5 cm. in its transverse diameter, and a marked increase had occurred in the radiability of both lung fields. The breathing continued to be shallow and the patient failed to make a further improvement. Twenty-one hours later respiration became slower and more shallow and the patient died of respiratory failure. A few moist râles were still heard over the chest but there was no recurrence of the widespread edema present before treatment. The cause of edema in his case seemed more closely related to the factor of increased permeability due to inflammation and anoxemia, perhaps accentuated by prontylin. Left ventricular failure may have been a secondary contributory factor.

Discussion

The cases that have just been reviewed indicate that positive pressure respiration may be used as an effective therapeutic procedure in acute edema of the lungs. The primary illness in which pulmonary edema occurs as a complication is frequently of such severity that an ultimate recovery cannot always be expected. However, there are cases as moribund as occurred in this series in which a clearance of pulmonary edema allows the patient opportunity to recover from the primary illness.

The pathogenesis of acute edema of the lungs is a varied one. The factors involved may be listed as follows: 1. Left ventricular failure. 2. Increased permeability of the pulmonary capillaries. 3. (*a*) A persisting pathologically elevated negative pressure within the chest, or (*b*) an abrupt termination of expiratory effort and a consequent loss of the backward pressure on the pulmonary capillaries. In case 1 the essential factor appeared to be left ventricular failure. Right ventricular failure was also present. Following removal of the thyroid gland the patient developed a thyroid crisis which was the exciting cause of cardiac failure the day after operation. The pulse became extremely rapid and in small volume. The blood pressure dropped to as low as 80 systolic and 60 diastolic, the venous pressure climbed to 280 mm. of water. Moist râles appeared in both lungs and gurgling was heard from the throat. It would seem likely that failure

of the left ventricle was responsible for backing up of blood in the lungs, increased hydrostatic pressure outward from the distended capillaries and finally exudation of serum. Since some anoxemia and capillary distention were also present, an additional factor may have been increased permeability of the lung. The marked elevation in venous pressure indicated an associated failure of the right ventricle. The swift clearance of pulmonary edema following the administration of a pressure of 7 cm. of water exerted a direct opposing force on the pulmonary capillaries, counteracting their tendency to ooze serum. The effect of positive pressure within the chest was also to retard the entrance of blood into the right heart and relieve the left ventricle as well as the right. As a result breathing became deep and easy, the lungs were clear and the circulation markedly improved. The venous pressure fell to 125 mm. In this instance, there was for a temporary period not only a clearance of pulmonary edema but a restoration of some degree of function of both the left and right ventricle.

In case 5 a man 72 years old on the fourth day following a prostatectomy developed broncho-pneumonia associated with cardiac insufficiency and edema of the lungs. In this case there were probably two factors at work, left ventricular failure and an increased capillary permeability due to pneumonic inflammation, anoxemia and capillary distention.

Case 4 was a woman of 37 years of age who suffered from massive consolidation of both lungs due to pneumococcus type 5. There was a blood stream infection with the same organism. Development of edema in her case seemed to be associated with increased capillary permeability due to inflammation and anoxemia. The fact that the pulse volume was extremely small with a rate of 150 and that the blood pressure dropped from 160 systolic and 85 diastolic to 110 systolic and 50 diastolic suggested that left ventricular failure was a contributory cause.

In case 2 a man of 50 years developed acute broncho-pneumonia following a hemorrhage from tuberculous lesion. On the fourth day, acute pulmonary edema developed accompanied by the signs of heart failure. The pulse mounted to 150 and was of small volume. The liver was palpable two fingers below the costal margin. In this case, left ventricular failure appeared to be the precipitating cause with increased permeability, due to inflammation and anoxemia, as the contributing factor. The clearance of pulmonary edema, the fall in pulse rate to 100 and the disappearance of other signs of cardiac failure, which took place in this patient, indicated that positive pressure respiration exerted its effect both as a physical force opposing a further tendency of the capillaries to ooze serum and as a restoration of cardiac function by limiting the volume of blood handled by the heart. The fact that 12 hours later pressure could be removed without recurrence of edema was added evidence that the essential cause of the edema was left ventricular failure.

The cases that have just been reviewed have some similarity to the experimental production of pulmonary edema following intravenous injec-

tion of adrenalin. In this type of edema our experimental evidence suggests that retarding the flow of blood into the right heart, thus enabling the heart to deal with a smaller volume, is of value in helping it to regain its function. The action of positive pressure in this respect is comparable to tourniqueting the extremities which is a therapeutic procedure of value in pulmonary edema.

In case 8, a man with widespread carcinoma of the lungs who developed broncho-pneumonia, the onset of edema of the lungs appeared to be associated with an increased permeability of the pulmonary capillaries as the most likely essential factor, with left ventricular failure as a contributing cause. One hour after positive pressure respiration was begun roentgen-rays showed a marked increase in radiability of both lung fields and a decrease in the transverse diameter of the heart of 1.5 cm. In his case not all of the moist râles in the lungs disappeared but the clinical improvement was at first quite marked. In case 6, a young woman with pneumonia due to the Friedländer bacillus, positive respiration was followed by a diminution of the loud moist râles over the anterior chest but not by any change in the crepitating râles. In another patient (whose case history is not reported in this paper), a clinical diagnosis of acute pulmonary edema following bronchopneumonia was not confirmed by autopsy. A woman of 54 years of age was ill for seven days with fever, cough and dyspnea. On physical examination, scattered moist râles were present over both chests from the onset of illness. She had long-standing mitral valvular disease with enlarged heart. On the seventh day of disease, severe dyspnea developed, accompanied by loud moist râles over the anterior chest and gurgling noises emanating from the throat. After three hours of positive respiration, 6.0 cm. positive pressure being employed in the hood, the right anterior chest was free from râles during inspiration, although loud moist râles could still be heard over the left anterior chest. There was an initial clinical improvement during the first eight hours of treatment which was followed by a progressive weakening of the patient and death 12 hours later. At autopsy, no pulmonary edema was found; the bronchi were filled with purulent exudate. The moist râles evidently had their origin in the bronchi and were apparently due to inflammatory exudate and not a serous transudation. Although the inspiratory dyspnea was relieved by distention of the lungs from without, there was only a partial clearing of the widespread signs of moisture.

The effectiveness of positive respiration seems more pronounced in the cases in which serous oozing is present and less noticeable in those in which inflammatory exudate is the cause of the râles in the chest. In the majority of cases of pneumonia, the onset of pulmonary edema is not accompanied by a prolonged circulation time, according to King and his collaborators,[28] which would suggest that pulmonary congestion due to heart failure is not the precipitating cause of the condition. However, more cases of pulmonary edema in pneumonia will have to be studied before the value of this treat-

ment can be determined. The most convincing and dramatic response to positive pressure respiration has occurred in those patients in whom some degree of failure of the left heart seemed clinically evident. In cases 3 and 7, the cause of pulmonary edema appeared to be different from that in the group just discussed. A predisposing factor seemed to be the previous presence of a high negative pressure within the chest due to severe inspiratory dyspnea, which may be compared to the development of pulmonary edema in animals subjected to respiration against a narrow orifice or against negative pressure.

In the discussion on the experimental production of edema that occurred after tracheal stenosis it was shown that the intrapleural negative pressure might increase to 10 times the normal value and that the heightened negative pressure exerted a suction action on the pulmonary capillaries. The same influence aided the inflow of blood into the right heart and hindered the exit of blood from the chest into the extra-thoracic aorta; thus, the factor of pulmonary congestion was added. In severe asthma the same mechanical influence takes place. The senior author has on one occasion demonstrated a markedly elevated negative pressure (— 17 cm. of water) in a case of severe asthma.

There is another important factor in the development of pulmonary edema in the two cases now being discussed. In each of them it will be remembered that the respiration rate decreased to two per minute. In case 7, three doses of morphine were given during the night. By depressing the respiratory center, the respiratory rate was not only markedly decreased but there was a marked diminution in the force of respiration. The ventilation of the lungs was, therefore, markedly diminished with the result that severe anoxemia was present, which is itself a factor in increasing capillary permeability. There is, however, still another factor that seems to be significant, namely, a sudden loss of a previously existing positive pressure against the pulmonary capillaries due to the patient's own expiratory efforts. The prolonged expiration of the patient with asthma results in an increased positive pressure between the site of bronchial constriction and alveolar capillaries. When this high positive pressure is abruptly terminated, the pulmonary capillaries become immediately more permeable.

It has long been known that in patients in whom laryngeal obstruction has existed for a considerable period, the provision of an unrestricted airway by tracheotomy is regularly followed by an outpouring of edema fluid from the lungs and bronchi into the trachea, which requires aspiration and suction at half hour to one hour intervals for many days and sometimes weeks. Woodman [29] showed that when the patient, immediately after trachectomy, was made to exhale under a positive pressure comparable to that present prior to the relief of the obstruction that edema fluid would not collect in the trachea. Kernan and Barach [30] treated three patients who began to show this characteristic filling of trachea and bronchi with edema fluid by the application of positive pressure during the expiratory cycle. The pres-

sure at the beginning of treatment was 7 cm. of water. This was gradually lowered during a two day period when the pressure was removed without any recurrence of edema fluid in the trachea. In one of these patients who had carcinoma of the lung there was the additional complication of hemorrhage. In this case after three hours of respiration against positive pressure there was not only an absence of edema fluid but the bleeding had stopped. This suggests that positive pressure may be used for cases of hemorrhage from the lung of capillary or venous origin.

There is, therefore, definite evidence that the sudden removal of a previously existing backward pressure on the pulmonary capillaries is followed by an increased permeability of the capillary wall and that the reëstablishment of this positive pressure comparable to what the patient had become accustomed to stops the leakage of serum. In patients with asthma the use of morphine in doses which markedly diminish the respiratory effort has, therefore, the danger of precipitating edema of the lungs. The sudden development of pulmonary edema after aspiration of pleural effusion may be due at least in part to sudden removal of a relative positive pressure and exposure of certain lung alveoli to resumption of negative pressure.

The senior author has already suggested that the expiratory grunt in lobar pneumonia has the physiological advantage of maintaining increased positive pressure against the alveolar capillaries at the beginning of expiration. That this grunting respiration is not simply a subjective complaint on the part of the patient but has the functional significance of preventing pulmonary edema was suggested by the observation of a case of lobar pneumonia that developed acute edema of the lungs following the administration of ½ grain of morphine. The patient had extensive involvement of both lungs due to pneumococcus type 3. He was in marked dyspnea and emitted a loud grunt at the start of expiration. After the administration of morphine the patient's respiration became shallow and slow without any grunt. He went to sleep and one hour afterwards had generalized edema of the lungs.

It has also been pointed out that patients with emphysema frequently partially close their lips during expiration and find that their breathing is made easier than when the mouth is open. We have made use of this observation in the treatment of patients with chronic asthma of moderate degree suggesting to the patient that he arbitrarily increase the resistance to the egress of air during expiration. In many instances a therapeutic exercise of this character pursued for three to five minutes will terminate an attack of wheezing, indicating that this backward distending pressure on the bronchioles tends to keep them patent. Certain areas of the lungs may have become accessible to ventilation, which previously were shut off by collapsed ducts or thin webs of mucus.

We do not mean to condemn completely the use of morphine for asthma or pneumonia since a moderate decrease in pulmonary ventilation relieves inspiratory dyspnea and lowers the negative intrapleural pressure. Doses

which exert a markedly depressive influence on the respiratory center have, however, the dangers which we have just described. It is of interest in this connection that Prickman [31] has also reported a case of asthma that became moribund after the administration of morphine and that finally recovered with the inhalation of helium and oxygen.

Although we have no clinical or experimental observations on the production of acute pulmonary edema through irritant gases it may be pointed out that the earliest case on record in which positive pressure respiration was used was in a patient who developed edema of the lungs following ingestion and inhalation of carbolic acid. In this remarkable report there was a clearance of edema after an hour's treatment.[5] This manifestly suggests its use in the treatment of pulmonary edema caused by irritant gases such as chlorine in commercial use and phosgene and other gases employed in war gas poisoning. This type of edema can be ascribed to increased permeability of the capillary wall due to irritation and inflammation.

Summary

Acute pulmonary edema has been studied from an experimental and clinical point of view. Three pathogenetic factors have been discussed:

1. Alterations in the pressure within the lung.
   a. A prolonged pathologically elevated negative chest pressure.
   b. An abrupt termination of backward pressure against the pulmonary capillaries.
2. Left ventricular failure.
3. Increased permeability of the capillary walls.

Following the production of tracheal stenosis it has been shown that edema of the lungs takes place associated with a marked elevation in intrapleural negative pressure. The pathological physiology thus produced exerts a two-fold influence:

a. A direct suction action on the pulmonary capillaries increasing the tendency to ooze serum through their walls.

b. A promotion of the inlet of blood into the right heart and a retardation of the flow of blood from the chest into the extrathoracic aorta, factors which increase pulmonary congestion. These physiological events are comparable to what takes place clinically in asthma and dyspnea due to obstructive lesions in the respiratory tubal passages.

As a result of large doses of morphine respiratory effort may be abruptly diminished. Although this makes for a reduction of the intrapleural negative pressure during inspiration, it also takes away the backward pressure which has been previously exerted against the capillaries lining the alveolar walls, as the patient attempts to deliver air through narrow bronchi and bronchioles. Expiration is proportionately much longer than inspiration and the removal of this accustomed back pressure has been found to result in pulmonary edema. Similarly, the removal of long standing obstruction

of the larynx by tracheotomy has been shown to result in an oozing of sero-mucous fluid. The application of positive pressure restores the accustomed backwardly directed pressure and prevents further oozing of serum from the capillary walls.

The experimental production of pulmonary edema in rabbits after intravenous injection of adrenalin has been shown to be due mainly to a left ventricular failure. Under these circumstances no elevation of the negative pressure within the intrapleural cavity was found. It was shown that the left heart was contracted, that the right heart was dilated; disproportion between the output of the two ventricles was, therefore, assumed. A marked passive congestion takes place in these animals followed first by passage of red corpuscles and later serum into the alveolar cells. An increased hydrostatic pressure in the pulmonary capillaries may be assumed under these circumstances to be the main factor, contributory factors being increased capillary permeability due to anoxemia and distention of the capillary walls. This type of experimental pulmonary edema appears to be comparable to that which follows left ventricular failure in clinical disease.

Concerning the third factor, there is evidence that anoxemia, inflammation, and distention of the walls of the capillaries increase capillary permeability. In cases exposed to irritant gases it may be assumed that increase in capillary permeability due to irritation and inflammation is of predominant importance.

Physiological observations were made on the effect of positive pressure respiration on normal subjects, on patients with congestive heart failure and a miscellaneous group. It was shown that when respiration is conducted under a positive pressure of 6 cm. of water normal individuals show a slight elevation in venous pressure, approximately 20 mm. of water and a prolongation of the circulation time of approximately 3½ seconds. In patients with congestive heart failure the venous pressure is increased, in some instances as much as 60 mm. of water and the circulation time may be prolonged 10 to 15 seconds. The heart under these circumstances deals with a smaller volume of blood, due to the fact that the positive pressure within the chest prevents the customary entrance of blood into the right auricle. Explanation of the difference between the behavior of normal subjects and persons with congestive heart failure was listed as follows:

1. The diminished elasticity of the congested lung prevents a compensating rise in negative pressure within the chest which is theoretically possible for the normal individual.

2. The positive pressure within the chest creates a greater interference with diastolic filling of the diseased heart, as compared to the normal.

The marked prolongation of circulation time found in some cardiac patients is not necessarily looked upon as a harmful influence since the decreased volume of blood with which the heart works may be helpful in restoring its function, despite the fact that greater back pressure is present in the systemic veins. Tourniquets applied to the extremities similarly

reduce the amount of blood entering the heart, a procedure which has been found of special value in treating edema of the lungs and "cardiac asthma."

The use of positive pressure respiration in 8 clinical cases of edema of the lungs is described. The effect of the procedure was in most instances a swift clearance of edema and a betterment of the state of circulation. The function of positive pressure in these cases, as in the experimental production of pulmonary edema, was to exert a direct opposing physical force on the external capillary wall tending to counteract the tendency to ooze serum and to decrease the inlet of blood into the right heart, in that way diminishing pulmonary congestion and permitting the heart to work on a smaller volume of blood. An attempt was made to discuss the importance of the factors which have been outlined in each individual case.

Conclusion

Acute pulmonary edema has been studied from an experimental and clinical point of view. In cases of respiratory obstruction the pathologically elevated negative pressure within the chest exerts a suction action on the pulmonary capillaries resulting in a tendency to ooze serum through their walls. Expiration against a constricted bronchial passageway maintains a backward pressure against the pulmonary capillary wall, inhibiting the leakage of edema fluid. A sudden termination of obstructive dyspnea, through excessive doses of morphine or as a consequence of tracheotomy, may be followed by edema fluid in the tracheo-bronchial tree. Positive pressure respiration has been found clinically helpful in the treatment of pulmonary edema associated with respiratory obstruction.

The pathogenesis of acute pulmonary edema arising as a complication of heart failure seems best explained by the original hypothesis of Welch: "A disproportion between the working power of the left ventricle and of the right ventricle of such character that the resistance being the same the left heart is unable to expel in a unit of time the same quantity of blood as the right heart." Positive pressure decreases the amount of blood entering the right heart and in that way diminishes pulmonary congestion and facilitates the clearing of pulmonary edema. When the lungs are distended from without by positive pressure there are the additional effects (*a*) a lowering of the negative pressure within the chest during inspiration and (*b*) a direct opposing physical pressure on the pulmonary capillaries, especially during expiration.

When pulmonary edema is due to irritation and inflammation, resulting in an increased permeability of the pulmonary capillary walls, positive pressure respiration is at times less effective in clearing the signs of edema.

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A SURVEY OF THE SO-CALLED HEMOLYTIC ANEMIAS *

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Introduction

Pernicious Anemia and the Hemolytic Anemias. Within the past few years, the problem of Addisonian pernicious anemia has been clarified by brilliant deductions and investigations until today, as a result, we have a satisfactory understanding not only of the mechanism of normal blood formation and of the several disturbances of this process which may lead to the same disease picture, but also of the method of action of the replacement therapy which acts so specifically and marvelously to save the lives of such patients. This is indeed a triumph to make us proud of those who accomplished this achievement.

During this same period, interest in the anemias which arise from increase in erythrocyte destruction has not been lacking, but unfortunately no corresponding progress has been made. Of course, something has been learned about individual forms such as hemolytic ictero-anemia and sickle cell anemia and a few additional forms of acute anemia from intense blood destruction have been identified. A little also has been learned of the process of hemolysis itself, of the relation of the reticulo-endothelial system to erythrocyte destruction and of the cycle of pigment metabolism, but there are still huge gaps in our knowledge of the fundamental process of erythrocyte destruction. From the clinical side we are still dealing with individual entities and we lack any better common basis for grouping these various anemias together under the term "hemolytic anemias" than a belief that they result from increased blood destruction although they may differ widely in the mechanism and location of that destruction.

It is true that we have learned a great deal about pernicious anemia, but it may be that even about that disease there is more to be discovered. One does not have to go very far back in memory to reach the days when pernicious anemia was defined as an hemolytic anemia with abnormal red cell formation, and I can well remember hearing discussions as to whether a patient with pernicious anemia exhibited sufficient evidence of hemolysis to justify the removal of the spleen. We all spoke glibly of the hemolytic and the aplastic types of pernicious anemia and we actually did seem to benefit some of the more hemolytic cases by splenectomy. I can recall several such patients and I wonder what they would today be diagnosed.

Undoubtedly there is an increased red cell destruction in pernicious anemia as is evidenced by the patient's yellow color, the increased urobilin output and the enlargement of the spleen. This increased hemolysis is

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thought to occur because the red cells which are produced by the pernicious anemia bone marrow are abnormal and are, therefore, more liable to destruction either by wear and tear, by phagocytosis or by true hemolysis. Nevertheless, we do not any longer include pernicious anemia among the hemolytic anemias, but it is interesting that the recent observations of Rhoads at the Rockefeller Institute tend again to place emphasis on the hemolytic aspect of this disease.

I have opened this survey of the hemolytic anemias with these remarks on pernicious anemia to point out the lack of clear separation between the various groups of anemias. It is, for this reason, that I used the term "so-called hemolytic anemias" in my title. We use the term pernicious anemia, dyshemopoietic anemia, deficiency anemia, aplastic anemia on the one hand and the term hemolytic anemia on the other—but we must remember that we are naming only what we believe to be the chief but possibly not the only factor in the pathogenesis of any one form. The separation between the two groups is not as distinct as we are apt to think. Inherently any disturbance of erythrocyte production will be reflected in erythrocyte destruction; any alteration in destruction will react on production. If the cells formed in the bone marrow are fragile, short-lived or liable to destruction by the normal red cell destroying mechanism of the body, then obviously increased hemolysis will occur with secondary hyperplasia of the blood destroying tissues; on the other hand, if abnormally rapid red cell destruction takes place, the bone marrow must, as long as it can, compensate by increased erythropoiesis and the cells put into circulation will surely be immature and may be below standard in other ways as well. And so a vicious circle tends to be established.

Each type of anemia will disturb both functions of what Krumbhaar named the "hemolytopoietic system." Furthermore, if it is the newly formed red cells which are destroyed and if this destruction occurs chiefly in the bone marrow by the cells of the reticulo-endothelial system, which as you know is distributed in the bone marrow as well as in the lymph nodes, liver and spleen, then the separation between disturbed production and increased destruction becomes even more difficult. One can arrive at a *reductio ad absurdum* if one wishes, by narrowing the problem down to whether the red cells die as it were *in utero* or are slaughtered by a sort of hemolytic Herod promptly after birth. It is the preponderance of the process, or the assumed initial fault which determines whether a given form of anemia is placed in one or the other group. Many remain in doubt. We are concerned at the time with those termed "hemolytic" and it is proper for us, therefore, to review our knowledge of the fate of the red blood cells in the body.

Normal Erythrocyte Destruction. Before proceeding to discuss the mechanisms of excessive destruction of red cells which lead to the various hemolytic anemias, we should consider the fate of the erythrocyte in the normal. Three methods of red cell destruction are recognized—phago-

cytosis by the cells of the reticulo-endothelial system, especially in the spleen; destruction by some hemolytic agent or condition of the plasma; and dissolution by simple wear and tear. Of these three methods, it is the third which in the normal would seem to be the physiologic fate of the red cells. Best [1] states that approximately one billion erythrocytes wear out every minute and must, of course, be replaced to keep the unit numbers of circulating red cells constant. Even in the normal there is some phagocytosis by the splenic cells and other cells of the reticulo-endothelial system but this is thought not to affect healthy erythrocytes. The spleen has been called the graveyard but not the slaughter house of the erythrocyte. Nothing is known as to the fate of the stroma and pigment of a red cell which happens to break up at a distance from the spleen and liver which are the chief collectors of reticulo-endothelial phagocytes, but reticulo-endothelial cells are present in all lymph nodes and in small numbers are widely scattered through the body.

It is said that, as a rule, hemolysis of erythrocytes in the strict meaning of the word does not occur in the normal, because there is no demonstrable hemoglobin in the normal blood plasma. However, this may be faulty reasoning based on tests not sufficiently delicate, for if erythrocytes break down at a distance from their graveyard, pigment must be liberated into the plasma. It is, of course, possible that local conditions as for example in the spleen, may so alter the pH, the electrolyte pattern or the osmotic potentialities of the blood plasma as to predispose to the final breakdown there of aged or weakened corpuscles. One can assume, for example, that the blood returning from the stomach during acid secretion is altered in its reaction and in its electrolyte pattern. I have long been tempted to speculate on this point for the gastric vein which drains the stomach runs a curiously long course and eventually empties into the splenic vein or sometimes directly into the portal vein. If only this altered blood entered the spleen, the theory would be easy. For the present, however, we cannot go behind the accepted view that hemolysis does not occur in the normal. Of one thing we can be sure and that is that whatever the method of red cell destruction, the body carefully preserves for re-use the iron, the pigment and probably the other components of the erythrocytes, and that probably the stimulus to red cell production is to be found in the products of red cell disintegration.

Hemolysis and Hemolysins. When we turn to consider hemolysis as it occurs in vitro and in vivo under a great variety of conditions, we find at once that we must not think of all hemolysis of erythrocytes as identical in mechanism, nor as a simple bursting of a liquid-containing cell with escape of its contents as the term hemolysis might seem to imply. It is important to remember that several methods of erythrocyte dissolution are included under this term hemolysis and that when one turns to the use of the term hemolytic anemia nothing more is implied than that the anemia results from increased erythrocyte destruction whether by phagocytosis or other means.

Perhaps it may not seem important in a consideration of the hemolytic

anemias for us to review the various methods by which different types of agents bring about destruction of erythrocytes, but it is important that we should not allow our familiarity with the action of hypotonic salt solution as a hemolytic agent to lead us to visualize all hemolytic processes as a simple matter of imbibition of fluid with a swelling of the cell and an assumption of a more and more spherical shape until rupture occurs. We suspect that that is the mechanism at work in certain hemolytic anemias but in others we feel sure that the method of destruction is far different and may or may not resemble one of the other methods which can be observed in vitro. For example, such chemical hemolysins as ether, chloroform, benzene and alcohol dissolve the envelope of the corpuscle and its stroma; bile salts and saponin also dissolve the stroma; acids act as does hypotonic salt solution and so do alkalies except that some also dissolve the stroma. Then there are the specific hemolysins such as are active in the hemolysis following a foreign blood transfusion and in the hemolytic system employed in the Wassermann test. Toxic substances without number may act as hemolysins including such widely differing agents as bacterial toxins, snake venom and even cold in susceptible persons who exhibit the Donath phenomenon. Even this list is far from complete and not all act similarly—for example, cobra venom acts by removing the unsaturated fatty acid from the lecithin molecule thus producing lyso-lecithin which is a violent hemolytic agent. When we come to consider the hemolytic anemias we must keep our minds open as to the methods by which the excessive red cell destruction may be caused. In some instances, it will be as obvious as in malaria, in others the weakness of the red cells apparently renders them easy victims to the normal destructive processes, in still others the presence of a known powerful toxin will seem to explain the pictures, but the process will not be the same in each nor will it be clear in all.

Hemolytic Anemias According to Mechanism of Hemolysis

If we attempt to group the well-known forms of hemolytic anemia according to the pathogenesis of the increased red cell destruction, we find something like the following.

Table I

1. Fault in the Erythrocyte.
   - (*a*) Hemolytic ictero-anemia.
   - (*b*) Sickle cell anemia.
   - (*c*) Hemolytic feature of pernicious anemia.
2. Parasitic Destruction of Erythrocyte.
   - (*a*) Malaria.
   - (*b*) Oroya fever.
3. Allergic Hemolysis.
   - (*a*) Favism.
   - (*b*) Occasional drug sensitivity: Sulphanilamide, for example.
4. Chemical Agents.
   - (*a*) Exogenous—acetanilid, lead, snake venom.
   - (*b*) Endogenous:
     1. By bile salts in infants with jaundice?
     2. Altered plasma pH.
   - (*c*) Conditioned—indol in dogs on deficient diet.

5. Bacterial Toxin.
   (*a*) *B. Welchii* infection.
   (*b*) Unidentified infection as in some cases of acute hemolytic anemia (Lederer)?
6. Mechanism Unknown and not Surely Hemolytic.
   Cooley's anemia.
   Erythroblastoses of infancy.
   Carcinomatosis??
7. Specific Hemolysins.
   Following transfusion of incompatible blood.
8. Physical Agents Such as Cold.
   Paroxysmal hemoglobinuria.
9. Excessive Destruction in Reticuloendothelial System.
   Reticulo-endotheliosis; Hodgkin's disease.
10. Phagocytosis by Leukocytes.
    So-called "phagocytic anemia."

Obviously any such classification is open to criticism and no two persons would adopt exactly the same arrangement. Some of the groupings are fairly certain, others very uncertain. Everyone, I think, would agree in attributing the increased blood destruction of hemolytic ictero-anemia and of sickle cell anemia to the obvious abnormality of the red blood cells of patients with these conditions and this is probably correct. Yet it should be pointed out that although the red cells of ictero-anemia are fragile in hypotonic salt solution and habitually possess a spherical shape such as erythrocytes assume as they approach dissolution in hypotonic solution, we do not know where or how these so-called spherocytes meet their end in the circulating blood. Nor do we know what it is that brings about the sudden crises of hemolysis that characterize both ictero-anemia and sickle cell anemia. Sometimes even a slight intercurrent infection precipitates such a crisis of hemolysis and makes one wonder whether with the infection a bacterial toxin enters the blood and produces an added hemolytic action, or whether there occurs with the fever some change in the reaction or electrolyte pattern of the plasma, or merely a speeding up of the usual destructive function of the tissue phagocytes. It is a reasonable but unproved assumption that the increased red cell destruction of these diseases is wholly due to a weakness of the cells themselves. Such a weakness is demonstrable in ictero-anemia but not in sickle cell anemia, although the cells in both are obviously abnormal. To which is added the further assumption that the enlarged spleen of ictero-anemia with its great increase in reticulo-endothelial phagocytes is a secondary feature responding to the need of disposing of the enormous number of dying erythrocytes.

In malaria and Oroya fever, the mechanism of red cell destruction by the parasites appears obvious. If it is true, as has been reported in bird malaria, that the plasmodium attacks only youthful reticulated red cells, it is interesting to realize that the bone marrow's response to the blood destruction, floods the circulation with the very type of young cells on which the plasmodium thrives.

Favism appears to be the perfect example of allergic hemolysis—for the violent red cell destruction in this condition seems not to follow the first eat-

ing of the favus bean but only subsequent ingestions, or even inhalations of the odor of the plant. It would seem that a specific hemolysin must be elaborated in such individuals. The behavior of sulphanilamide in the occasional production of acute hemolytic anemia suggests at least that the factor of idiosyncrasy enters in in some cases. So perhaps this cause of hemolytic anemia should be classed as allergic rather than with the rest of the many exogenous chemical agents which quite regularly produce hemolysis. In this latter group, one may use acetanilid and lead as examples. The beautiful experimental work of Rhoads [2] and his collaborators has demonstrated that certain chemicals may cause hemolysis only when special conditions prevail—as for example, indol in dogs on a certain type of deficient diet—the indol apparently merely accelerating the action of other hemolysins (Ponder [3]).

Some very interesting studies by Ham [4] in Minot's laboratory and by Dacie, Israels and Wilkinson [5] in England, shed further light on the matter of hemolysis by changes in the chemistry of the blood. In some cases of chronic hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria, a syndrome which has been named after its two Italian describers Marchiafava and Micheli, Ham was able to demonstrate that the nocturnal hemolysis was related to the elevation of the carbon dioxide content of the arterial blood and the associated decrease in the pH which occurs in sleep. Counteracting this shift with sodium bicarbonate reduced the hemoglobinuria, while ammonium chloride, as might be anticipated, increased the physiologic shift and the hemoglobinuria. This would seem to prove very prettily that the red cells of these patients are abnormally susceptible to hemolysis in plasma of increased acidity but within the physiologic range of pH variation. Unfortunately, alkali medication, while temporarily beneficial did not cure the condition and excessive blood destruction followed the omission of the sodium bicarbonate. An interesting review of some cases of this syndrome appeared recently in the Quarterly Journal of Medicine.[6]

Bacterial toxins such as that of the gas bacillus of Welch, undoubtedly cause hemolytic anemia in some infections, but there is much doubt and speculation as to how active in this respect other less virulent bacteria are. It is tempting but unjustified to attribute the anemia of many infections to a hypothetical hemolytic toxin. Similarly it is not known whether an infection is responsible for all or some of the instances of so-called acute hemolytic anemia of Lederer and others. Even less is known as to the cause and mechanism of Cooley's anemia and of the so-called erythroblastoses of infancy. Some deny the presence of hemolysis in these conditions but it seems to me that the picture is so like that of other known hemolytic anemias that we should accept them in our hemolytic group even if we do not know the agent or the method of increased erythrocyte destruction.

The remaining types of hemolysis need little discussion here. The mechanism of transfusion hemolysis is familiar to all of us, while hemolysis induced by cold usually in syphilitic subjects, the hemolytic anemia in Hodg-

kin's disease, and the occasional case of so-called phagocytic anemia are so rare as not to justify more than a passing mention.

Again we are impressed with the variety of methods by which destruction of erythrocytes is occasioned and the great number of conditions in which some increased blood destruction occurs. Of course, the entire picture of hemolytic anemia does not appear in all of these patients, but potentially it might and at times does.

Common Features of Hemolytic Anemia. So far in this review we have been considering the mechanism which acts in the production of the increased red cell destruction which is the essential characteristic of any anemia which is to be classed as hemolytic. We must now pass on to some consideration of the clinical and laboratory phenomena which are common to this group of conditions; then to some of the manifestations peculiar to the more important individual entities and finally to the principles of treatment which apply to the hemolytic anemias in general.

Although there are many mechanisms of increased blood destruction and many hemolytic anemias, there is a remarkable constancy in the manifestations common to the entire group. These fall naturally into three groups: (1) the immediate evidences of the increased blood destruction; (2) the compensatory hyperplasia and hyperactivity of the reticulo-endothelial system and (3) the evidences of regenerative activity of the hemopoietic blood producing tissues.

Of course, these phenomena will appear in different degrees and combinations in different varieties of hemolytic anemia, depending upon the severity and rapidity of the blood destruction, the duration of the process, the integrity of the blood forming tissues, et cetera. But by and large, every case of hemolytic anemia shows to some degree the same phenomena and so we may properly speak of the symptom complex of hemolytic anemia.

Blood destruction liberates hemoglobin into the plasma in amounts proportionate to the number of erythrocytes destroyed. This pigment in amounts far in excess of that derived from normal degrees of blood destruction, tends to follow the normal course, being absorbed by the Kupffer cells of the liver and other cells of the reticulo-endothelial system to be excreted as bile, largely reabsorbed from the bowel, and re-utilized. However, the amount of reabsorbed pigment now in the form of urobilinogen is apt to be so great that some tinges the skin of the patient and some escapes through the kidneys in the urine. A yellowish facies and urobilin in the urine thus become common features of any hemolytic process of sufficient severity or chronicity, as was noted at the beginning of this paper, in discussing pernicious anemia. If the hemolysis is of still higher grade and the liberated hemoglobin reaches a figure of 0.7 gram per 100 c.c. of circulating blood, hemoglobin itself tends to pass the kidney filter and hemoglobinuria, another phenomenon common to many hemolytic processes, appears, as for example in black water fever and in the so-called Marchiafava-Micheli syndrome of nocturnal hemoglobinuria. It may be worth mention-

ing that from the point of view of these phenomena, there is little or no difference between an acute and primary attack of hemolysis with the rapid appearance of anemia, and an episode of increased blood destruction such as occurs in the course of a chronic hemolytic anemia, such as ictero-anemia or sickle cell anemia.

The next feature common to hemolytic anemias is the hyperplasia of the reticulo-endothelial cells or to return to the usual simile of the graveyard—an enlargement of the cemetery. No doubt all the reticulo-endothelial system participates in this increased activity but we recognize it only in the enlargement of the spleen and perhaps the liver which occurs in almost every hemolytic process acute or chronic. The spleen is in man the largest mass of reticulo-endothelial cells and a demonstrable splenomegaly is accordingly expected in hemolytic anemias. Quickly before the question is asked, I must hasten to mention one important exception. The spleen is enlarged in sickle cell anemia only in the early stages and seems to go on to a reduced size as the disease progresses probably as a result of a fibrotic overgrowth, perhaps from irritation by phagocytized material.

Active regeneration of blood, or erythropoiesis, is another phenomenon characteristic of hemolytic anemia. This again varies greatly according to the rapidity of the blood destruction, the chronicity of the process, the condition of the bone marrow and indeed the age of the patient. In all instances, however, the changes in the blood picture are in the same direction —first occurs anemia or an increase in anemia, then after a variable time lag there appear immature red cells—erythroblasts and reticulocytes—and to some measure the anemia is halted or conquered. At the same time the number of white cells is increased by the appearance of more and more immature members of the marrow series—polymorphonuclears and myelocytes, probably due to the effect of active erythropoiesis on the adjoining leukopoietic centers in the marrow.

For many years, it has been assumed that the urobilin output and the evidences of regeneration in the blood bear some relationship in a rough way to the degree of blood destruction. Josephs [7] at Johns Hopkins has been attempting recently to express these relationships in the form of an equilibrium. The many variables in the problem make this a very difficult matter. For example, any disturbance of blood production in either direction will confuse the picture as, for example, such an increase in red cell production as becomes established in hemolytic ictero-anemia or, on the other hand, such failure of bone marrow function as may eventually result. Josephs has also found it difficult to work out the balance when there is any great number of nucleated red cells—for while such erythroblasts are, of course, immature forms analogous to reticulated red cells, yet erythroblastosis may well be a deviation from normal red cell production and not merely a more active regeneration. As we will see when we come to discuss the individual hemolytic anemias, some exhibit more erythroblastosis than do others. It seems proper, however, to include both those that do exhibit marked

erythroblastosis and those in which blood regeneration is evidenced by the more usual reticulocytosis, together in the group of hemolytic anemias.

Leukocytosis of cells of the marrow series, as has been mentioned, is a common feature of the blood picture of hemolytic anemia during the regenerative stage. This again is very variable and tends to be more marked in infants in whose blood there may appear not only a considerable number of youthful neutrophiles—a shift to the left—but even myelocytes. It is important to remember this neutrophile leukocytosis of hemolytic episodes and avoid the error of using it as an argument in favor of an infectious basis for the hemolytic process in a given case.

There is still another feature of a number of the hemolytic anemias which deserves comment. This is the presence of a strong familial and hereditary tendency governing the incidence of certain of the diseases in this group. Hemolytic ictero-anemia and sickle cell anemia are the familiar exemplars of this fact but the erythroblastic anemias of infancy and Cooley's anemia of infants of Mediterranean stock also show a familial tendency which, however, may be due more to conditions of life than to any true hereditary fault. At any rate, the presence of a congenital hereditary fault is not recognized in these syndromes as it is in ictero-anemia and sickle cell anemia. Heredity is an important influence in many diseases of the hematolyto-poietic system and is not limited to these hemolytic anemias. For this reason, this aspect of the hemolytic anemias should not be too much emphasized. It is, however, worth noting in passing that blood groupings and allergic sensitivities which may play a part in certain hemolytic processes are also determined by heredity.

Certain of the Hemolytic Anemias. Let us now briefly consider certain of the individual hemolytic anemias: (*a*) Hemolytic ictero-anemia which was formerly called "hemolytic icterus" or "acholuric jaundice" deserves special mention for it is so characteristic of the whole group. In this disease, the increased blood destruction seems to depend upon an hereditary congenital abnormality of the erythrocytes which we recognize by the lessened resistance of these cells to hypotonic salt solution in vitro and by their spherical shape. Apparently this defect renders these cells liable to premature hemolysis by the normal erythrocyte destroying mechanisms of the body, and excessive blood destruction is readily induced if anything occurs to increase the conditions favorable to hemolysis. Depending, therefore, on these factors the members of a family with red cells of this type may vary much in their manifestations of disease. One individual will be in apparent health with no anemia and only a slight yellowness of the skin, a slight urobilinuria and a slight enlargement of the spleen. Another will be moderately anemic while a third may be in extreme anemia with fever, a huge spleen, distinct jaundice of skin and blood serum and with much bile pigment and urobilin in the urine. This variability in the activity of blood destruction explains the faulty view formerly held, that there was an acquired form of this disease—the true explanation being that such individuals al-

though born with the same susceptible cells never exhibited the clinical phenomena of increased red cell destruction perhaps until middle age. Often careful questioning will, however, elicit a history of an attack or attacks of previous yellowness which were mistakenly diagnosed catarrhal jaundice, or the family history will contain the record of the death of a child with the picture of an acute infection and severe anemia.

Apparently the margin of safety against hemolysis of the erythrocyte in such individuals must be very narrow for as we have said any intercurrent infection may throw such an individual into a violent erythroclastic crisis which the French term a "crisis of deglobulization." Characteristically the patient has many such episodes of greatly increased blood destruction before coming to the curative operation of splenectomy. Death, if it occurs, does so as a rule from intense anemia after blood regeneration has failed to keep pace with the excessive blood destruction.

The blood picture reveals evidence of the rapid red cell production by the presence of increased numbers of young reticulated erythrocytes—sometimes three-quarters of all the red cells are still youthful enough to exhibit polychromatophilia in the usual stained spread and reticulocytosis when stained with brilliant cresyl blue or some other of the vital stains. Nucleated red cells may be present with the reticulocytosis but not as a rule in the enormous numbers which may appear in certain other hemolytic anemias. Usually many of the red cells in the stained spread appear small and deeply stained. Less high reticulocyte percentages will, of course, be found if hemolysis lessens and eventually in severe cases when the long overworked bone marrow fails, the blood picture may be that of aplastic anemia.

Splenectomy greatly reduces the total of the reticuloendothelial blood destroying tissue and so lessens the degree of hemolysis; it has little or no effect upon the inherent red cell abnormality which being inherited persists through life. It is amazing how much improvement may follow splenectomy in the face of the continuance of the fundamental fault in the erythrocyte.

(*b*) Sickle cell anemia resembles hemolytic ictero-anemia in many ways. Both are characterized by a congenital hereditary familial defect in erythropoiesis. Both are characterized by crises of hemolysis with the same symptoms, the same evidences of increased blood destruction, the same evidences of blood regeneration. Individuals with either of these congenital red cell abnormalities may exist for years without any crisis of hemolysis and without anemia—or may succumb to intense hemolytic anemia. Both may show some degree of bone absorption but this phenomenon is far more marked in certain other hemolytic anemias and will be discussed later.

Differences between the two diseases do, however, exist. The sickle cell fault is found almost, if not exclusively, in those of the negro race; the spleen of sickle cell anemia while enlarged at first, tends to become fibrosed, contracted and is often markedly adherent to the neighboring peritoneum. Also in the sickle cell crisis of hemolysis there is more apt to be abdominal

pain; leg ulcers are more common and gall stones less common than in hemolytic ictero-anemia.

Of course, the red cell fault differs in the two; the erythrocytes of sicklemia are not less resistant than normal to hypotonic salt solution, but do exhibit the typical sickle shape—sometimes in the stained spread and always upon standing in the hanging drop or under any conditions which lower oxygen tension. Even less than in hemolytic ictero-anemia can one see the connection between the abnormality of the red cells and their excessive destruction.

(*c*) So-called paroxysmal hemoglobinuria has been discussed and is only mentioned again because of the many similarities which the individual crises of hemolysis of this syndrome bear to those of hemolytic anemia and sickle cell anemia. It is unfortunate that the name "paroxysmal hemoglobinuria" has been attached to this syndrome for the hemoglobinuria is only an outward and visible sign of a severe hemolytic episode. As we have said, this condition occurs almost exclusively in late syphilis; there is a specific hemolysin present in the blood and the crises of hemolysis are precipitated by exposure to cold. It must be remembered that hemoglobinuria may occur in any hemolytic episode if the amount of liberated hemoglobin is sufficient. Paroxysmal hemoglobinuria is a special case.

(*d*) Next we must mention the so-called idiopathic hemolytic anemias, both acute and chronic. Obviously from their name little or nothing is known concerning their etiology, nor is there any obvious congenital fault in the erythrocytes nor any recognized hemolysin or chemical change in the plasma. Thus even in a field where we know little, these syndromes deserve the term "idiopathic" which is an admission of even greater ignorance. Various eponymics are also applied to these anemias of which Lederer's name is the most commonly used.

Again there is a great deal of similarity between the attack of such acute idiopathic hemolytic anemia and the individual episode of hemolysis in one of the other hemolytic anemias we have discussed. Perhaps such an anemia sometimes is the actual unrecognized cause of the so-called idiopathic anemia, in other instances there may be an unidentified acute infection producing an active hemolytic toxin; in still others some allergic incident similar to that in favism may be responsible. Certainly, we must remember not to stress too much the fever and the leukocytosis as evidences of the presence of infection for these symptoms are usually present in hemolytic episodes of non-infectious nature. For the present, we had better admit our ignorance and continue to call these cases "idiopathic" unless we accept as applicable to the whole group what Ham[4] found in a few cases. As I told you, he demonstrated in cases of chronic hemolytic anemia that the red cells were neither unduly fragile in hypotonic salt solution nor of the sickle cell variety, but were abnormally susceptible to hemolysis in plasma of increased acidity within the normal range as occurs during sleep. If this evidence proves to be widely applicable, it supplies us with a further red cell fault

which would make these cases more nearly analogous to the better understood hemolytic anemias.

(*e*) The only remaining hemolytic anemia entities which need to be discussed are the erythroblastic anemias of infants and Cooley's anemia of infancy and childhood. There is no agreement as to whether these conditions are truly hemolytic; Magner,[8] for example, in a very recent textbook of hematology, places them all under dyshemopoietic anemias. However, it seems to me that the resemblances which these conditions bear to the better known hemolytic anemias are too great to be ignored. In both the erythroblastoses of infancy and Cooley's anemia, there is a familial incidence, jaundice, splenomegaly, anemia and a markedly regenerative blood picture with enormous numbers of nucleated red cells and young neutrophiles and myelocytes. No fault has, however, been demonstrated in the red blood cells although Caminopetros[9] claims that an increased resistance to hypertonic salt solution is just as constant in Cooley's anemia as the reverse is in hemolytic ictero-anemia. It is hard for me to believe that these anemias are not primarily hemolytic although those who take the opposite view stress the occasional absence of jaundice and the frequent failure to find urobilinogen in the urine. These objections do not seem very important to me, especially when we remember that it is necessary for bile to enter the bowel, there be converted into urobilinogen and then be reabsorbed into the blood, in order for urobilinogen to appear in the urine. In these infants, it may well be that this cycle is not completed.

(*f*) Miscellaneous. Time will not permit a discussion of the many other episodes of hemolysis from miscellaneous causes, which result in more or less anemia—but it should be said that in general they all resemble the acute crisis of hemolysis in hemolytic ictero-anemia or sickle cell anemia. The acute hemolysis after transfusion of incompatible blood is one example of this; the erythroblastic blood picture of chronic acetanilid intoxication resembles that of certain other hemolytic anemias; the acute hemolytic anemia produced by sulphanilamide resembles a blood crisis in ictero-anemia. It is helpful to keep these resemblances in mind.

The Bone Marrow and Bone Changes in Hemolytic Anemia

I have carefully avoided trying to describe the bone marrow in the various conditions we have been discussing. I have done this because it is my opinion that there is little to be gained from doing so. During active blood regeneration in response to blood destruction the marrow is red and hyperplastic but we cannot yet surely distinguish the erythropoietic process which floods the circulating blood with reticulocytes from that which frees enormous numbers of nucleated red cells into blood stream. In infancy, we are not surprised to find hemopoiesis still going on in the liver and spleen as well as in the marrow. But when we have made these statements we have said

about all we can and we are not any nearer an understanding of the matter. For the present, it seems better to speak in terms of physiologic processes.

In speaking of the bone marrow it is interesting to remember that osteoporotic changes in the bones themselves occur in a number of the hemolytic anemias. These have been described in hemolytic ictero-anemia, sickle cell anemia and especially in Cooley's anemia. It seems probable that this osteoporosis which appears chiefly in the bones of the skull and the long bones is an evidence of the invasive action of the very markedly hyperplastic red marrow in such cases. In patients with less hemolysis and therefore less active red blood cell production, or in those in whom the process had not continued sufficiently long, the bone changes may be absent. Such bone changes may, therefore, be non-specific and merely the result of very active hemopoiesis and are to be included among the features common to the severe, continuing cases of hemolytic anemia of any kind. This should be subject to experimental proof.

Prognosis and Treatment. We come next to the question of the principles of prognosis and treatment of the group of hemolytic anemias. It is easy to say of prognosis, as mathematicians say of so many things, that it is a function of a number of variables. This, of course, is the gist of the matter for the variables are many and include the continuance or cessation of the hemolytic activity; the severity of anemia and the regenerative ability of the bone marrow. If the factor causing the excessive hemolysis can be eliminated, the prognosis will depend upon the degree of anemia already established and the possibility of carrying on with transfusions until red cell production has caught up with the needs of the body. If, on the other hand, one cannot remove or reduce the hemolysis then obviously the prognosis is bad and often eventually hopeless. Individuals with sickle cell anemia have a poor prognosis and the majority die before reaching middle age. On the other hand, hemolytic ictero-anemia is compatible with long life in those in whom there occurs little hemolysis or in whom hemolysis is reduced by splenectomy. In Cooley's anemia, the outcome is always fatal and the prognosis in the erythroblastic anemias of infancy is almost as grave.

The same principles of treatment apply to many of the hemolytic anemias. If hemolysis is severe and anemia is increasing, it is obvious that repeated transfusions may be indicated whether the hemolysis is an isolated incident as in sulphanilamide intoxication or is one episode of a hemolytic ictero-anemia.

Of course, everything must be done to remove the cause, if possible, but where this resides in a congenital fault of the red cells it is apparently impossible to do so. In hemolytic ictero-anemia, therefore, one must accept the continued presence of susceptible red cells but one is able to cut down the hemolysis by removing, by splenectomy, the chief collection of reticulo-endothelial cells. Very beneficial in hemolytic ictero-anemia, this operation is of no value in sickle cell anemia nor apparently in most cases of chronic hemolytic anemia with nocturnal hemoglobinuria; although in an occa-

sional case, splenectomy does seem to give benefit. This led Ham to speculate as to whether the spleen does not provide a region with sluggish circulation and, therefore, a pH sufficiently lowered to predispose to hemolysis of susceptible cells—another example of conditioned hemolysis. Cooley believes splenectomy may prolong life in the disease to which his name is attached, but others do not agree.

It is interesting that in instances of hemolysis following transfusion of incompatible blood there tends to occur severe kidney disturbance with anuria and often with death. This may be prevented or treated, with success in some cases, by the administration of alkali. No such interruption of renal function occurs with the hemoglobinuria which occasionally appears in the episodes of hemolysis of other hemolytic anemias except occasionally in malarial black water fever.

Again, we find ourselves considering treatment in terms of attempted correction of a disturbed physiologic process. Specific treatment we lack. What we can do depends upon our proper interpretation of the mechanisms bringing about the anemia in each patient.

Conclusion

We have arrived at the end of our survey of the hemolytic anemias and as is customary we think back over what has been said in the hope of arriving at some definite and useful conclusions. As I do this, I realize that there is little constructive or helpful in what has been said. It has, I am afraid, been destructive rather than constructive. We have found that our knowledge, understanding and treatment of the hemolytic anemias are in a far less satisfactory state than they are in pernicious anemia and the deficiency anemias. We have seen that there is no universal agreement as to which anemias are hemolytic and we have learned that there are a number of different mechanisms of red cell destruction, all of which we casually group together under the term hemolysis. And we are led to suspect that often two agents are active in producing the red cell destruction—one acting only when the cells have been conditioned by the other. We have reviewed a few of the more distinct entities only to find that we are not sure even in these, of the pathogenesis and that our treatment is satisfactory in but few and not specific in any. It is a discouraging state of affairs.

On the bright side, however, a few claims may be made. We have discovered that the anemias grouped together under the term hemolytic have many features in common in their causation, symptoms, manifestation of blood destruction, in the evidences of hyperactivity or erythrocyte production, in the blood pictures and in the principles governing prognosis and treatment. By an appreciation of these group behaviors and by an interpretation of these diseases in terms of disturbed physiology, it would seem that there is hope for a clearer understanding of the whole problem. By visualizing the blood destroying and blood producing mechanisms and tissues as interrelated parts of one system we are led to anticipate and understand

many of the manifestations of a disorder which may in its name suggest a disturbance of but one-half of the hemolytopoietic balance. Ultimate understanding awaits further knowledge and to this end—research in the laboratory and the hospital; study of experimental anemia in animals; and of the disease in man must be continued.

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THE CURVES OF THYROXINE DECAY IN MYXEDEMA AND OF IODINE RESPONSE IN THYROTOXICOSIS: THEIR SIMILARITY AND ITS POSSIBLE SIGNIFICANCE *

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IN 1924 Segall and Means [1] published a curve which represented the average of the basal metabolic responses of a series of thyrotoxic patients to subtotal thyroidectomy, without the previous administration of iodine. They called this the detoxication curve. About a year later Starr, Segall and Means [2] published a curve similarly obtained and constructed, representing the basal metabolic response of a similar series of thyrotoxic patients to the oral administration of iodine.†

The impressive feature of these two curves was that, save for a postoperative hump on the thyroidectomy curve, the two were, in shape and rate of descent, close to identical.

This identity, or close similarity, of the basal metabolic response of the thyrotoxic person to removal of most of his thyroid, on the one hand, and to the flooding of his system with iodine, on the other, has ever since greatly interested us. At the present time we believe that we can throw some light on its significance.

It is pertinent to point out first, however, that in 1928 Means, Thompson and Thompson [4] reported further observations on the response of thyrotoxic patients to iodine and drew therefrom certain conclusions. Among these conclusions were the following: (*a*) that iodine causes a characteristic diminution in the intensity of the intoxication in toxic goiter; (*b*) that such a response is obtainable at any stage of the disease; and (*c*) that iodine does not affect the course of the disease. A diagrammatic schema was provided which indicated these relationships.‡

Studies on the iodine response in toxic goiter have been continued and have shown that as biologic reactions go it is an amazingly constant and predictable affair. We have published from time to time composite curves for groups of cases arranged on the basis of preiodine metabolic rate. In figures 1 and 2 will be found our latest study of this sort. The individual curves were those from unselected cases of toxic goiter making iodine responses, in which a level of metabolism had been satisfactorily observed

* From the Thyroid Clinic of the Massachusetts General Hospital. Presented in abstract to the Association of American Physicians, Atlantic City, May 1937. Received for publication May 16, 1938.

† For graphs, please see the original papers, or MEANS, J. H.: The thyroid and its diseases, 1937, Lippincott,[3] figure 42.

‡ See original paper or MEANS, J. H.: The thyroid and its diseases, Lippincott,[3] 1937, figures 47, 48 and 49.

before iodine administration was begun. Figure 1 shows the actual composite for each group (separation into groups being on the basis of each ten-point interval of preiodine basal metabolic rate) together with the number of cases from which the group average curve was made. The average curve weighted, for the entire lot is shown by the heavy line.

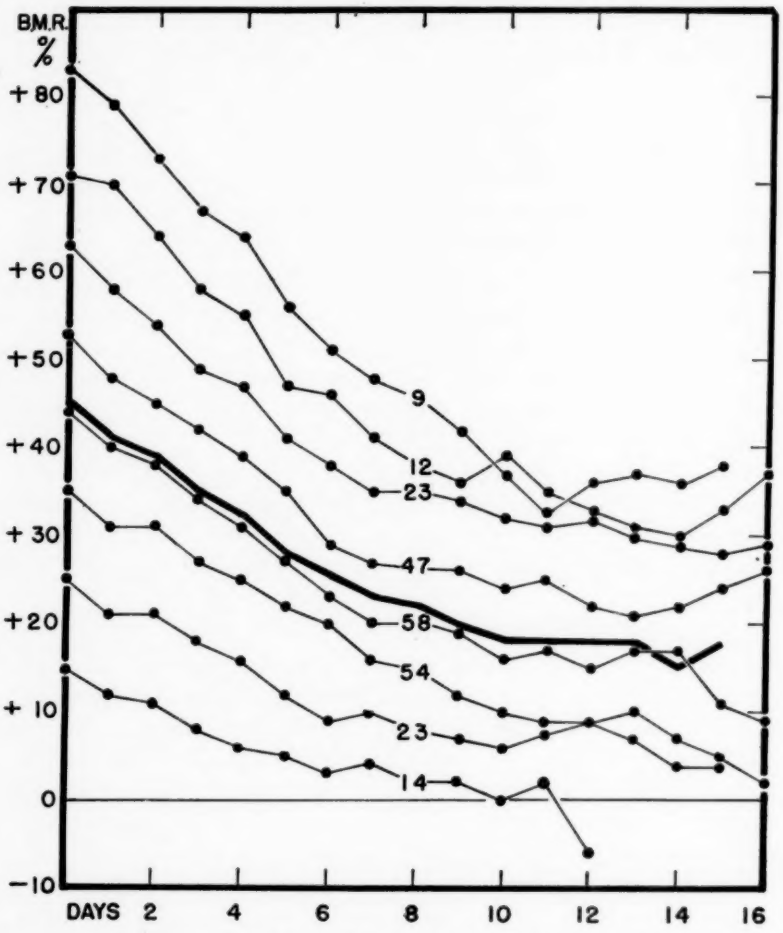

FIG. 1. Iodine response in 240 cases of toxic goiter. Divided into groups in accordance with preiodine basal metabolic rate level. (Years 1930–35, inclusive.) The lines are the composite for each group. The heavy line is the weighted average for the entire group. The numbers on the curves indicate the number of individual cases in each group.

The curves of figure 1, including the weighted average, or composite, were replotted on semilogarithmic paper. On this, up to the tenth to twelfth day they approached straight descending lines; after that, they tended to level off. Absolutely straight lines were then drawn, as closely as possible, through the points up to the twelfth day, and these in turn were replotted on ordinary coördinate paper. The result was the family of

smooth curves shown in figure 2. This graph may be taken to represent what may be reasonably called the standard iodine response.

Another basal metabolic phenomenon of precise and predictable nature is delineated by what Boothby [5, 6, 7, 8] and his co-workers have called the curve of thyroxine decay. This may be defined as the curve traced by the basal metabolism of a subject whose supply of thyroid hormone is suddenly interrupted. Such a cessation of hormone supply might occur when, in an athyreotic person maintained at a standard level of metabolism by thyroid,

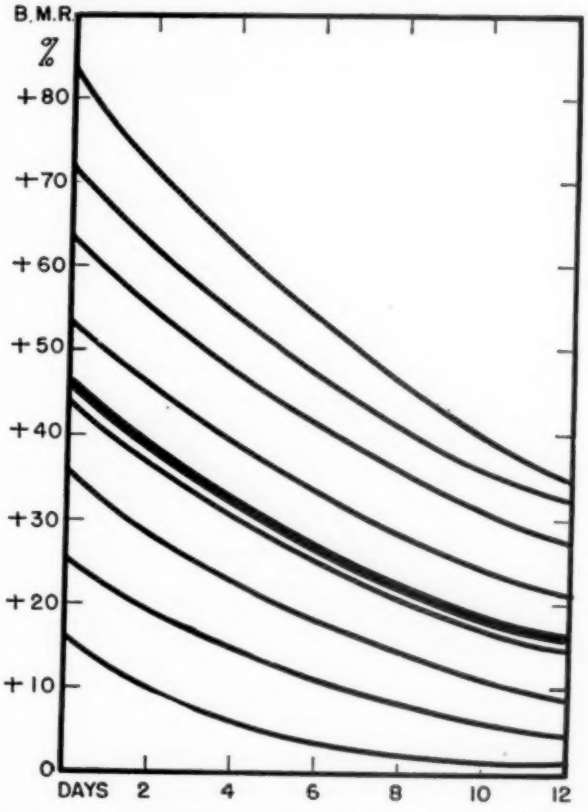

FIG. 2. Iodine response in toxic goiter. Same data as shown in figure 1, but smoothed as described in text.

the administration of thyroid was suddenly stopped, or when, in the case of a person possessed of a functioning thyroid, the gland was totally removed. A group of such curves is shown in figure 3. They are very similar in contour one to another. That is to say, stoppage of supply of thyroid hormone produces, as does iodinization, in thyrotoxic persons, an amazingly constant result.

It is to be noted that six of the curves in figure 3 are from an approximately standard level of metabolism. A composite has been made of these

six and is shown by a heavy line. Three curves starting above standard are also shown in figure 3 and a composite made of them is also indicated by a heavy line. When the point of origin of the upper composite curve is shifted so that standard metabolism falls on the zero day, then that portion of the composite above standard becomes merely the continuation of the composite of the lower six curves.

As in the case of the iodine response curves, the composite of the six decay curves was plotted on semilogarithmic paper. On this when deducting the limiting value of minus 40, or 60 per cent of standard, from each point, an essentially straight descending line is obtained.

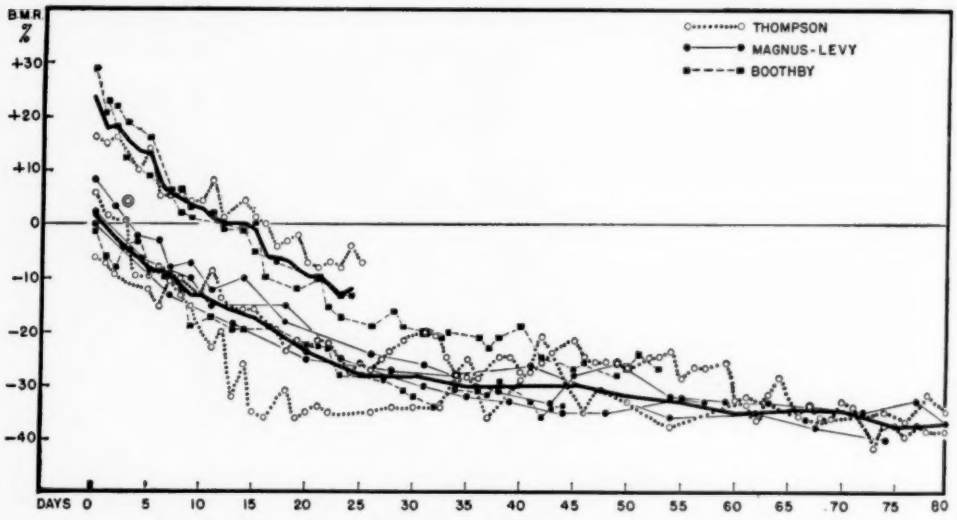

FIG. 3. Thyroxine decay in myxedema. Individual curves obtained by various observers, together with two composites, one for six curves starting near basal metabolic rate 0 and one for three curves in the neighborhood of basal metabolic rate plus + 20. If the latter is pushed to the left it will be found to form a natural continuation of the former.

The data of thyroxine decay and iodine response suggest curves of the type $y = C + Ae^{-kt}$ or so-called exhaustion curves. Here, y is the per cent of standard metabolism at any given time, t; C the per cent of standard metabolism which the curve approaches as a limiting value; A the increment of metabolism above the limiting value at an arbitrary zero day; and e^{-k} the exponential constant. In the case of thyroxine decay, the limiting value, C, is the myxedema level of minus 40, or 60 per cent of standard, and A becomes 40 if the zero day is arbitrarily chosen at 100 per cent (± 0) of standard. Thus the curve becomes $y = 60 + 40\ e^{-kt}$. It should be noted that the composite thyroxine decay curve starts at plus 2 in figure 3, but for convenience in calculation the zero day was shifted one day to the right to make it coincide with standard metabolism.

From the composite decay curve of figure 3, the value of k was calculated for each day. These values are more or less uniform up to the 35th day.

This corresponds to that portion of the curve which shows a steady descent and which approximates a straight line on semilogarithmic paper. The remainder of the curve levels off for a few days and then falls at a somewhat slower rate. Consequently the values of k for the first 35 days only were averaged and the average of 0.0421 used in the equation which becomes $y = 60 + 40\ e^{-0.0421t}$. The theoretical curve "T" described by this equation is shown in figure 4.

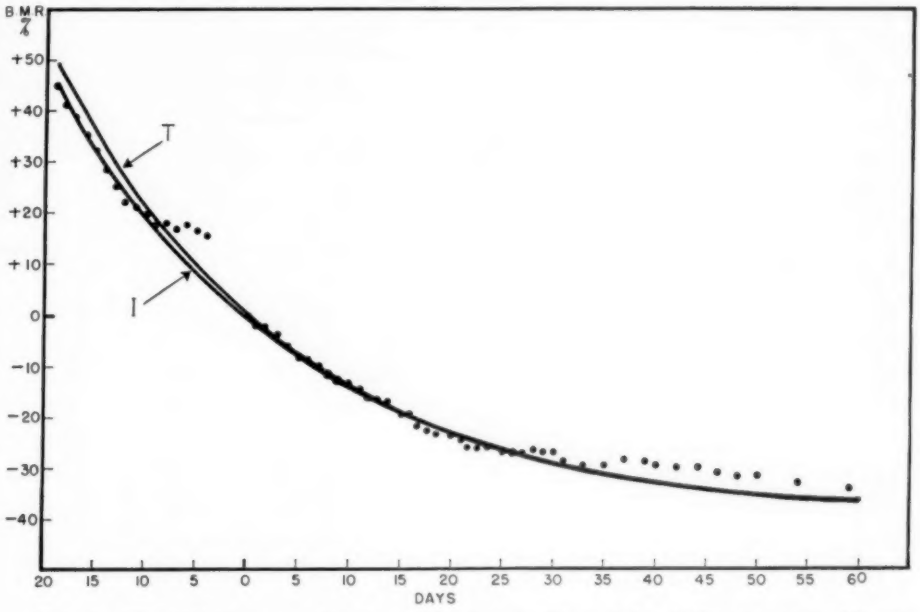

FIG. 4. Theoretical curves for thyroxine decay (T) and for iodine response (I), together with the actual points from which they were derived. Curve I was plotted so that basal metabolic rate $\pm$ 0 fell on the same day as basal metabolic rate $\pm$ 0 for Curve T.

In like manner the composite of iodine response may be represented by a similar equation. However, it is necessary to make one assumption, namely, that the rapidly falling metabolism produced by iodine, if uninterrupted by other factors, would eventually reach the myxedema level of minus 40. That would be true if the delivery of thyroid hormone to the blood were completely blocked by iodine for a considerable period of time. If this assumption holds, then C is 60 in this case also. The metabolism at zero day is 145 per cent and therefore $A = 85$. Thus the equation becomes $y = 60 + 85\ e^{-kt}$. The values of k were calculated for the first twelve days and found to vary from 0.0342 to 0.0480, the average being 0.0409. From the equation $y = 60 + 85\ e^{-0.0409t}$, the theoretical curve "I" is plotted in figure 4. It is almost identical to curve "T." This we consider a fact of great significance.

These two curves, "T" and "I," may also be constructed mechanically by plotting the data on semilogarithmic paper, after subtracting the limiting

value of 60 from every individual point and then drawing the best possible straight lines through the corresponding groups of points. The curve "*I*" is prolonged downward and the curve "*T*" upward. The straight lines and their prolongations are then replotted on ordinary coördinate paper. These are not shown graphically because they are so nearly identical to those shown in figure 4.

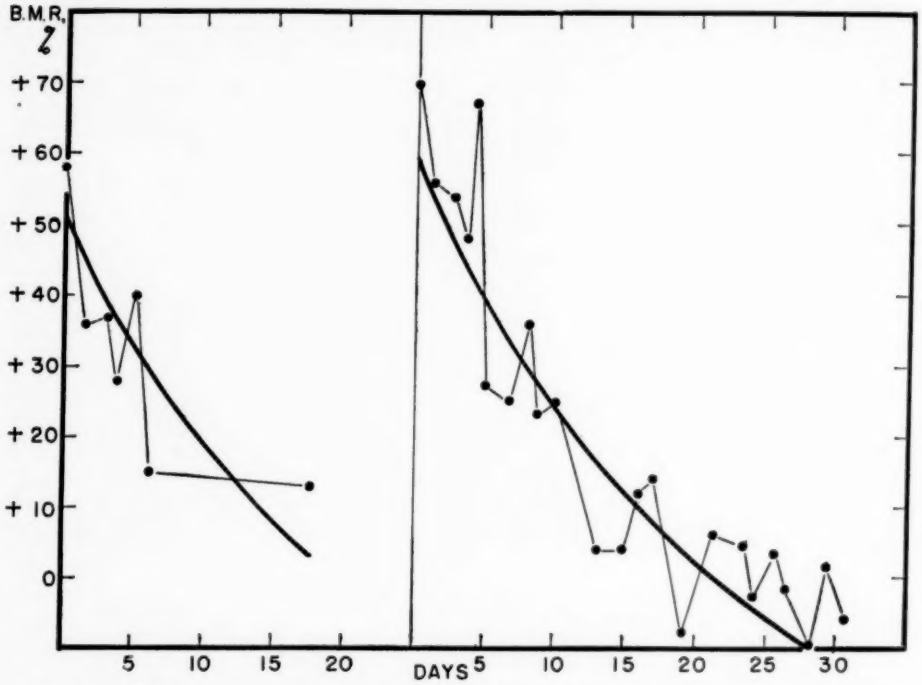

FIG. 5. Iodine response and thyroxine decay in same patient. On the left is shown the response to iodine when the patient was naturally thyrotoxic and on the right to cessation of thyroid administration when she was artificially thyrotoxic. To each of these for comparison is fitted Curve *T* from figure 4.

The curve "*T*" depicted in figure 4 is essentially similar to the thyroxine decay curves described by Boothby. In fact, it is composed in part of Boothby's data. The exponential equation described by the latter is similar to the one given above. These exhaustion curves, as Boothby contends, may describe a monomolecular type of reaction in which the reacting substance is the concentration of thyroid hormone in the tissues. However, an exponential curve or a straight line on semilogarithmic paper does not necessarily indicate a monomolecular reaction. On this point we concur with Rabinowich.[9] We have no means of deciding at present whether we are dealing here with a monomolecular reaction or not. The demonstration by Rabinowitch, that the values of the exponential constant, *k*, in one curve of Boothby's obtained between daily intervals, vary considerably, is not a valid argument against a monomolecular type of reaction. Experience in-

dicates that the decline in metabolism of any one myxedema patient does not follow a smooth curve. As the number of observations increases, the composite approaches a smooth curve. The values of k are bound to vary as much as the individual daily metabolic rates. In our own calculations the values of k up to 35 days were relatively constant.

The actual data from which curves "*T*" and "*I*" were constructed are, for comparison, also shown in figure 4. The iodine response data follow curve "*I*" very closely until the twelfth day is reached; then they flatten out. The thyroxine decay data follow curve "*T*" very closely, except for an interval between the fortieth and fifty-fifth day. Here the actual data fall above the theoretical curve. This discrepancy may be the result of the small number of observations in this segment of the curve.

A recent case has provided us with some rather unique information which bears upon the relation of iodine response and thyroxine decay.

The patient Miss L. (M. G. H. 340286), aged 26 years, entered the hospital with moderately severe, classic exophthalmic goiter. The curve obtained on iodinization is shown in figure 5. She had a subtotal thyroidectomy and postoperatively ran a substandard rate. Psychosis also developed. The Psychiatric Service, to which she was transferred, raised her metabolic rate to about plus 60 by administration of thyroxine (in order to discover whether this would alter her psychosis). On cessation of this medication a decay curve from this high level was obtained. It also is shown in figure 5. The striking feature is that the two curves are essentially alike, although one is due to iodinization when the patient was spontaneously thyrotoxic and the other to the stopping of thyroid administration when she was artificially thyrotoxic.

Discussion

Let us now review these facts and consider what they may signify.

First, we have the fact that in spontaneous thyrotoxicosis, taking out most of the thyroid gland has the same, or close to the same, metabolic result as iodinization.

Next, we find that the composite curve of thyroxine decay in myxedematous persons and the composite curve of iodine response in thyrotoxic persons appear to be natural segments of a single long curve extending from a high level of basal metabolic rate to a level in the neighborhood of minus 40. At least the upward prolongation of the thyroxine decay curve gives a close approximation to the iodine response curve and the downward prolongation of the iodine response curve gives a close approximation to the thyroxine decay curve.*

Finally, we have an example in one and the same person, Miss L., of the quantitative similarity of the metabolic response to iodine at a time when she was spontaneously thyrotoxic, to that of cessation of thyroid

* Preliminary statements of these relationships have been made in previous publications.[10, 11]

medication when she was artificially so. We know that the metabolic curve delineating one of these events was actually one of iodine response, that delineating the other actually one of thyroxine decay, and they are quite alike.

These several facts, all of which indicate the identity, or at least the close similarity, between the effect of iodinization of the thyrotoxic patient and thyroidectomy, and between iodine response and thyroxine decay, seem to us consistent with the theory that iodine response in spontaneous thyrotoxicosis actually is dependent on thyroxine decay, that the effect of iodine in spontaneous thyrotoxicosis is to block the delivery of thyroid hormone from gland to body, and serves for a time at least to deprive the subject of hormone as effectively as removal of the hormone factory. This corresponds to the period during which thyroid follicles are filling up with newly-formed thyroid hormone as the result of shift in chemical equilibrium produced by iodine.[12]

Further collateral evidence of thyroid block might be obtained by analysis of blood and other tissues for concentration of thyroid hormone. Thus far direct attempts to measure thyroid hormone have been difficult, although Lunde,[13] in 1929, reported that the alcohol-insoluble fraction of iodine decreased as the inorganic iodide increased in the blood of patients receiving iodine. Indirect evidence of this decrease in thyroid hormone in the blood has recently been suggested by Salter and Craig.[14] They obtained a "vicarious" or "indirect" elevation of metabolism of surviving tissues treated with blood from hyperthyroid patients. As the basal metabolic rate fell in response to iodine therapy, this "vicarious" metabolic response also declined.

One reservation is in order. Consider for a moment thyroxine decay from a high level. This may be observed either in the thyroidless (e.g. myxedematous) subject or in the normal subject. Should the basal metabolic rate of a totally thyroidless subject be raised to plus 60 by thyroid administration, his metabolism might be expected to fall, upon cessation of thyroid administration, along a curve like curve "*T*" in figure 4 until a level of about minus 40 basal metabolic rate had been reached. Should the basal metabolic rate of a normal subject be raised to plus 60, however, his basal metabolic rate might be expected to fall, indeed undoubtedly would fall, upon cessation of thyroid administration, along a curve which would start out along the course of curve "*T*," but which as it approached standard would flatten out, and assume a horizontal course in that neighborhood. This latter is essentially what the curve of iodine response in spontaneous thyrotoxicosis does.

In either of these cases, a course of pure thyroxine decay is approached but not attained. The obvious reason being that a factor other than thyroxine decay enters the picture. That is the power of the subject's thyroid gland to deliver hormone to the body and of this hormone so delivered to raise metabolism. In the thyroidless subject whose thyroid

medication is stopped the metabolism curve is smooth to its base in the substandard zone. It is throughout its entire course a curve of pure hormone decay. In the case of the normal subject, raised to plus 60 basal metabolic rate by thyroid feeding, however, there is a functioning thyroid gland present which will make hormone at a rate which will keep the basal metabolic rate at a near standard level. When thyroid medication is stopped the basal metabolic rate will at first drop along a pure decay curve, but then flatten out as the hormone contributed by the subject's own gland makes its effect apparent. The resulting curve under these circumstances is a pure decay curve in its upper portion only. It is a less simple curve than that displayed by the thyroidless subject. The iodine response curve in spontaneous thyrotoxicosis is of the former sort. It also tends to flatten out somewhere in the neighborhood of standard metabolic rate. It is equal to a pure thyroxine decay curve in its upper portion only. As the thyroid follicle resumes excreting thyroid hormone at a constant rate, a new equilibrium is established.

Conclusions

The basal metabolic rate curve of thyroid hormone decay has been shown to be closely similar to that of iodinization in spontaneous thyrotoxicosis in the following respects.

a. Iodinization and subtotal thyroidectomy without iodinization cause similar metabolic responses.

b. The composite iodine response curve of thyrotoxic persons forms a segment of the same curve as that traced by thyroxine decay in myxedematous persons.

c. In a single person identical metabolic curves were produced by iodinization when the subject was spontaneously thyrotoxic and by withdrawal of thyroid when she was artificially thyrotoxic.

On the basis of these facts the theory is advanced that iodine response in spontaneous thyrotoxicosis is in fact due to thyroxine decay; that the flooding of the system with iodine under such circumstances causes an interruption for a time of the delivery of new hormone from gland to body at large, and that hormone previously delivered decays at the same rate as in the thyroidless subject.

We wish to express our gratitude to Dr. C. R. Doering for help in the mathematical treatment of our data.

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HOW ACCURATE IS THE DIAGNOSIS OF FUNCTIONAL INDIGESTION? A STUDY OF 354 CASES *

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THE diagnosis of functional or nervous indigestion is made so frequently at present that it seems wise to determine, if possible, the accuracy with which the diagnosis is made. Many clinicians find that the majority of patients with dyspepsia who come under their observation fail to present any evidence of significant organic disease, and they are therefore of the opinion in such cases that the indigestion is functional or nervous in origin. In other cases a diagnosis of functional dyspepsia may simply represent the physician's inability for various reasons to discover an underlying organic disease to account for the symptoms.

That dyspepsia of functional or nervous origin is common is indicated by the studies made some years ago by Vanderhoof, Blackford and Dwyer and Foster in which it was found that of 7300 cases of indigestion, in approximately 25 per cent the dyspepsia was of functional origin. In approximately 20 per cent of the cases, systemic disease elsewhere than in the gastrointestinal tract accounted for the symptoms. In approximately 35 per cent of the cases, a reflex cause of the dyspepsia was found in disease of the accessory organs of the digestive tract, whereas in about 14 per cent of the cases there were organic lesions in the stomach and duodenum.

Little evidence has been produced to indicate the accuracy with which the diagnosis of nervous indigestion is made. In an attempt to evaluate this phase of the problem, we have studied the records of 354 patients who after examination at The Mayo Clinic received a diagnosis of functional or nervous indigestion or its equivalent and who were reëxamined at the clinic some years later.

In a somewhat similar study of 235 cases in which a diagnosis of chronic nervous exhaustion was made, Macy and Allen found that the diagnosis had been accurate in from 85 to 98 per cent of cases. The actual figure was approximately 94 per cent. In their study chronic nervous exhaustion was used to indicate a " long present, subjective sensation of tiredness, disproportionately exceeding the effort which produces it and which cannot be accounted for by organic disease. Weakness, lack of energy and ambition, nervousness, unrestful sleep, or insomnia, melancholia, tachycardia, and pains and aches in various parts of the body may be additional symptoms of the condition." It is of particular interest in relation to this

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study of dyspepsia of functional origin to note that in Macy and Allen's series the most frequent point of origin of the major symptoms was the gastrointestinal tract (38 per cent of cases) and that the symptoms most frequently noted were bloating and belching, soreness of the abdomen, constipation, eructation, and indefinite types of distress.

Material Studied

The records were studied in 354 cases in which the patients returned to the clinic for reëxamination an average of 7.33 years (table 1) after the

Table I

Interval between Original and Subsequent Examinations in 354 Cases

Interval, years	Cases	Per cent
Less than 5	18*	5.1
5	84	23.7
6	65	18.4
7	66	18.6
8	37	10.5
9	42	11.9
10–15	36	10.2
15–20	4	1.1
More than 20	2	0.6
Average 7.53	354	100.1

* In these cases the original diagnosis of functional dyspepsia was subsequently proved to be questionable or an error.

original diagnosis of nervous indigestion, functional dyspepsia, or its equivalent was made at the clinic. By selecting cases in which reëxamination was done on one or more occasions after a period of some years, we hoped to be able to trace the cases in which organic disease was a significant etiologic factor and in which it was apparently overlooked at the time of the original examination. It seems reasonable to believe that, if dyspepsia were due to unrecognized organic disease, after a period averaging seven years the development of symptoms and the results of examination would disclose the organic disease in the majority of cases. As Macy and Allen pointed out, the objections to such an assumption seem minor since it is the almost uniform tendency of organic disease to progress and to become more obvious or to improve and to lead to disappearance or diminution of symptoms.

Observations at Primary Examination

Character, Incidence and Duration of Symptoms. In this group of 354 cases there was a wide diversity of type and duration of symptoms and the clinical pictures resembled those observed in almost all types of gastrointestinal disease. It cannot be concluded readily that any group of symptoms is invariably the result of functional gastric disturbances. Belching, fullness and heaviness in the upper part of the abdomen after eating were

the most common symptoms. Nausea, vomiting, eructations of gastric content and relief of symptoms following administration of sodium bicarbonate, other alkalies, or food were next. Heartburn was present rather infrequently. More than half of the patients stated at the time of the original examination that they were nervous or the presence of this symptom was recorded by the examining physician. It has often been stated that symptoms which are functional in origin are characteristically constant in their occurrence. However, in a group of 138 cases in this study in which the constant or intermittent character of symptoms was noted, in 76 cases (55 per cent) the symptoms were present intermittently. The relation of symptoms to ingestion of food was clear cut in 87 per cent of those cases in which reference to the occurrence of symptoms during the digestive cycle was noted. The symptoms occurred before and after meals at widely varying intervals in this group of cases. Pain or discomfort in the epigastrium was present in half of the cases in which the situation of pain was noted; in other cases the pain was located in various parts of the abdomen and more rarely in the thorax, back and shoulders. The type of painful sensation frequently noted was burning; other patients described their discomfort as gnawing, dull, aching, sharp, cramp-like or colicky or as a soreness, or sense of pressure or heaviness.

The duration of symptoms at the time the original examination was made is given in table 2. In 299 cases (85 per cent) the symptoms had been present for at least one year and in many cases the symptoms had extended over a considerably longer period of time.

TABLE II

Duration of Symptoms before Original Diagnosis of Functional Dyspepsia in All Cases, with Reference to the Subsequent Diagnosis in Certain Cases

Duration, months	Total cases	Subsequent diagnosis		
		Duodenal ulcer	Gastric ulcer	Gall-bladder disease
Less than 1	6			1
1 to 2	4			
2 to 3	5	2		
3 to 6	16			1
6 to 12	24	2		1
Years				
1 to 2	49	2	1	2
2 to 3	32	3	1	
3 to 4	20	1		
4 to 5	17	1		1
5 to 10	64	4	3	3
10 to 20	53	3		
More than 20	35	1		
Not stated	29			1
	354	19	5	10

Physical and Laboratory Examinations. The results of physical examination in almost all instances were essentially negative except that nervousness, abdominal hyperesthesia and tenderness were observed occasionally.

Anemia was not a frequent finding. In 62.5 per cent of those cases in which the blood was examined the values for hemoglobin were more than 75 per cent (Dare).

Estimations of the levels of free hydrochloric acid in the gastric contents are given in table 3. A wide variation in the values for free hydrochloric acid was apparent and is about what one would expect to find in a group of normal individuals of the same age and sex.

TABLE III

Values for Free Hydrochloric Acid at the Time of the Original Diagnosis of Functional Dyspepsia with Reference to the Subsequent Diagnosis in Certain Cases

Free Hydrochloric Acid	Patients			Subsequent Diagnosis				
	Males	Females	Total	Duodenal Ulcer	Gastric Ulcer	Gall-bladder Disease		Carcinoma of the Stomach
						Questionable	Stones	
Absent	10	12	22	0	1	0	1	0
0–20*	16	16	32	0	1	2	0	1
20–50*	121	77	198	9	1	1	1	1
50*	64	15	79	8	1	1	3	0
No record	11	12	23	2	1	1	0	0

* Töpfer's method.

Roentgenologic examinations of the stomach were carried out in most of the cases and in the majority the findings were negative. In 23 cases the examination was not done, in three cases the results were indeterminate, and in two other cases a normally functioning gastro-enterostomy was found. Examination of the gall-bladder was performed in 90 cases; in 86 the gall-bladder appeared to be normal; in three cases it was reported to be poorly functioning, and in one case the result was indeterminate.

RESULTS OF SUBSEQUENT EXAMINATIONS

We have divided our cases into three groups: Group 1 consisted of cases in which organic disease was not present at the time of subsequent examination; group 2, of cases in which organic disease of the gastrointestinal tract was found at the time of a subsequent examination, and group 3 of cases in which, at the time of subsequent examination, organic disease was found elsewhere than in the gastrointestinal tract which it was felt may or may not have explained the original symptoms (table 4).

TABLE IV
Summary of Final Diagnosis

Group	Final Diagnosis	Cases	Per cent
1	Functional dyspepsia	303	85.6
2	Organic gastrointestinal diseases	39	11.0
3	Organic disease other than in gastrointestinal tract	12	3.4
Total		354	

Group 1. Organic Disease Not Found at the Time of Subsequent Examination. This group is composed of 303 cases (85.6 per cent of the entire group). All of these patients returned to the clinic at least five years (table 1) after the original examination at which time a diagnosis of functional or nervous indigestion had been made. In all of these cases the diagnosis originally made was confirmed at the time of the subsequent examination. Subsequent to the original examination many of these patients had not had symptoms referable to the gastrointestinal tract, other patients had observed an increase or no change in the symptoms, and in the remaining group of cases a diagnosis of functional dyspepsia—its equivalent, or of chronic nervous exhaustion or psychoneurosis was made at the time of the final examination.

This is in reality the least interesting of the three groups. The results suggest a diagnostic accuracy of at least 85.6 per cent for functional dyspepsia in this series. The original diagnosis usually rested on the clinical data which have been mentioned previously and which included evaluation of the gastrointestinal symptoms, the frequent nervous or apprehensive nature of the patient, and the negative results of laboratory and roentgenologic studies.

Group 2. Organic Disease of the Gastrointestinal Tract Found at Subsequent Examination. This group consists of 39 patients (11 per cent of the total, table 5). Eighteen of the patients in this group returned to the

TABLE V
Summary of Final Diagnosis in Group 2

Diagnosis	Male	Female	Total
Duodenal ulcer*	18	1	19
Gastric ulcer*	5	0	5
Disease of gall-bladder (proved)*	4	1	5
Disease of gall-bladder (suspected)*	1	4	5
Carcinoma of stomach	2	0	2
Congenital short esophagus	0	1	1
Diverticulosis of colon	0	1	1
Chronic ulcerative colitis	1	0	1
			39

* For time in years between original and subsequent diagnoses, see table 2.

clinic within five years of the time of their original examination (table 1) because their symptoms continued and in each instance, a diagnosis of an organic disease was made.

In 19 of the 39 cases a final diagnosis of duodenal ulcer was made and this represented the most common diagnostic error in the series. Other subsequent diagnoses in this group were gastric ulcer, cholecystic disease, carcinoma of the stomach, and so forth. Details concerning the cases in which each diagnosis was made are as follows:

Duodenal ulcer: Eleven of the 19 patients who had a final diagnosis of duodenal ulcer returned to the clinic within a period of five years. Eighteen of the 19 patients were men. Although it is possible that a duodenal ulcer was not present at the time of the original examination, in 14 of these cases the history was characteristic of peptic ulcer. In four cases in which the original story was atypical for duodenal ulcer, a questionable duodenal ulcer was encountered at the time of operation in one case and in two cases, roentgenologic examination was not made at the time of the initial examination. In one case the history only slightly resembled that of duodenal ulcer. In 16 of the 19 cases roentgenologic examination at the time of the first admission gave negative results; subsequently a duodenal ulcer was found. In 17 of these cases in which gastric analysis was made, free hydrochloric acid was present in the gastric content at the time of the original examination (table 3).

This evidence suggests that when a patient gives a characteristic history of duodenal ulcer, when free hydrochloric acid is present in the gastric content and when the duodenum appears normal roentgenologically, care must be exercised in making a diagnosis of functional dyspepsia.

Gastric ulcer: In five cases at the time of the subsequent examination a gastric ulcer was found. It is of interest to note that all of these patients were between 40 and 50 years of age at the time of the original examination, and that all of them at the time of the original examination gave histories similar to those of patients who have ulcer.

Cholecystic disease: Of the 354 cases in only three instances were gallstones found at a subsequent examination. In two other cases operations on the gall-bladder were performed and cholecystitis was found. In none of these cases does review of the original history reveal evidence of colic or jaundice; in fact, the dyspepsia recorded was of an indefinite type.

In five additional cases a final diagnosis was made of probable or questionable disease of the gall-bladder. In three of these cases at the time of the last examination roentgenologic studies of the gall-bladder revealed no abnormalities. The diagnosis of disease of the gall-bladder remains unverified in this group.

Carcinoma of the stomach: In two cases a diagnosis was eventually made of carcinoma of the stomach.

In one case the patient, a man aged 59 years, complained originally of a gnawing pain in the epigastrium two hours after meals over a period of

three to four months. The value for free hydrochloric acid in the gastric content (Töpfer's method) was 24 units and for total acid 44 units one hour after the Ewald meal. Roentgenologic study of the stomach gave negative results. Four years later the patient returned to the clinic with the same complaints and on roentgenologic examination was found to have an ulcerating carcinoma at the pyloric end of the stomach.

The second patient, a man aged 34 years, came to the clinic because of a dull epigastric ache which was relieved by the taking of food and which was of five years' duration. The values for free hydrochloric acid in the gastric juice (Töpfer's method) was 42 units and for total acid 58 units. Roentgenologic study of the stomach revealed nothing abnormal. A diagnosis was made of functional dyspepsia. Four years later the patient returned to the clinic, at which time he was found to have a carcinoma of the stomach which was resected.

Other types of organic disease of the gastrointestinal tract: In one case each a final diagnosis was made of congenital shortening of the esophagus, diverticulosis of the colon, and chronic ulcerative colitis. There is considerable doubt in the last two cases as to whether the original symptoms were caused by disease in the colon.

Group 3. Organic Disease Found Outside of the Gastrointestinal Tract at the Time of Subsequent Examination. There were 12 patients in this group (table 6). It is extremely difficult accurately to evaluate the relationship of the diseases eventually discovered to the digestive symptoms originally complained of. Gastrointestinal symptoms may occur in all of the diseases noted in this group but review of the histories in these cases shows only two in which a clear-cut relationship could be established between the symptoms originally complained of and the disease eventually discovered. In one case a subtotal thyroidectomy for exophthalmic goiter three years after the original diagnosis of functional dyspepsia led to complete relief of all gastrointestinal symptoms. In another instance review of the history

TABLE VI

Summary of Final Diagnosis in Group 3

Diagnosis	Cases	Time, Years*
Pernicious anemia	2	1 and 7
Heart disease	2	11 and 9
Syphilis	1	5
Arteriosclerosis	1	4
Hyperthyroidism	1	3
Myxedema	1	5
Kidney stone	1	6
Pulmonary tuberculosis	1	5
Nephritis	1	7
Pituitary tumor	1	6
	12	

* Between original and final diagnosis.

suggests that the original digestive symptoms could have resulted from a pituitary tumor which was found to be present after a period of six years. In one case the diagnosis of pernicious anemia was made one year following the original diagnosis of functional dyspepsia. At the time of the original diagnosis of dyspepsia this patient who was a woman aged 50 years complained that for three years she had experienced epigastric burning when the stomach was empty. Achlorhydria was present, roentgenologic study of the stomach did not give evidence of abnormality, the value for hemoglobin was 68 per cent (Dare), erythrocytes numbered 3,820,000 per cubic millimeter of blood, and the color index was 0.8. It is quite likely that pernicious anemia was present at the time of the original examination.

Comment

If one considers that the cases listed in groups 2 and 3 represent errors in the original diagnosis of functional dyspepsia or its equivalent, the proportion of error is 14.4 per cent, and the accuracy in diagnosis is 85.6 per cent. It is of interest to note that in a group of 354 cases in which a diagnosis of functional dyspepsia was made, examinations after a period averaging seven years revealed evidence of organic gastrointestinal disease in only 11 per cent. Whether it is logical to assume that in all these cases the organic disease was present at the time the original diagnosis was made and was responsible for the symptoms cannot be determined. In some instances, particularly in cases of duodenal or gastric ulcer, this seems likely. If to this group are added the 12 cases (3.4 per cent) in which final examination revealed evidence of a lesion elsewhere than in the gastrointestinal tract the maximal percentage of error is 14.4. It is probable that the actual percentage of error is less than this.

In the study of cases of chronic nervous exhaustion conducted by Macy and Allen, it is of interest to note that the accuracy of diagnosis was found to be between 85 and 98 per cent and actually to be about 94 per cent.

This study leads to the conclusion that when a diagnosis of functional dyspepsia is made after careful examination of the patient and his gastrointestinal tract, the likelihood that the diagnosis is correct is in the neighborhood of at least 85 to 89 per cent. This accuracy of diagnosis compares favorably with that of most other diseases. Analysis of this series of cases suggests that the lesions most likely to be overlooked or to be found or perhaps to develop over a period averaging seven years are duodenal and gastric ulcer and cholecystic disease. Concerning the possible sources of error it seems wise before making a diagnosis of functional indigestion to give much consideration to a patient who is a man and who presents a story suggestive of ulcer. In such cases a diagnosis of functional dyspepsia should be made only after a very thorough investigation, and then it is well to add the reservation that an unrecognized ulcer may be present or may develop subsequently.

It is hoped that as time goes on greater accuracy will be developed in the recognition of organic and functional disease of the gastrointestinal tract. This will be accomplished principally by careful study of patients, recognition of the fact that duodenal and gastric ulcer and disease of the gall-bladder may be overlooked more frequently than other gastrointestinal lesions, and that occasionally unrecognized systemic disease may account for vague or indefinite gastrointestinal symptoms.

In the last few years use of the gastroscope has added another diagnostic procedure which should prove of considerable value in elucidating the diagnostic problem of chronic indigestion. It has been stated that in clinics in which routine gastroscopic studies have been made by experienced observers there is an incidence of some type of chronic gastritis in 28 to 37 per cent of cases of chronic dyspepsia.

Summary

In an attempt to determine the accuracy with which the diagnosis of functional or nervous indigestion is made, we have studied the records of 354 patients who after examination at The Mayo Clinic received a diagnosis of functional or nervous indigestion or its equivalent and who returned and were reëxamined at the clinic an average of seven years later. The original diagnosis was confirmed in 303 cases (85.6 per cent). The most common sources of error were duodenal and gastric ulcer and disease of the gall-bladder. It seems reasonable to believe therefore that the diagnosis of functional indigestion can be made with considerable accuracy following a careful examination.

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CLINICAL EXPERIENCES WITH LONG-ACTING INSULIN IN AMBULATORY DIABETIC PATIENTS *

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Since the publication of Hagedorn's article [1] on protamine insulinate in January 1936, followed by the substitution of protamine zinc insulin for protamine insulinate as the result of the work of Scott and Fisher [2] and the introduction of a new crystalline insulin by Sahyun of Detroit, medical periodicals have been flooded with reports concerning the treatment of diabetes mellitus with these new long-acting insulins.

To review this literature would be superfluous indeed, since it has been adequately summarized in numerous previous articles. The reader interested in a comprehensive survey of the literature on this subject is referred to the papers of Joslin,[3] Wilder [4] and Ricketts.[5]

The advantages of the newer insulins with a prolonged hypoglycemic effect have been thoroughly established. They include a more constant, hence better physiologic, control of diabetes, a reduction in the number of daily injections of insulin and frequently a considerable reduction in the total daily insulin requirement. The various disadvantages accompanying the use of these new insulins have been discussed in detail in previous reports and will not be considered here. Suffice it to say that the magnitude of these disadvantages has steadily decreased with increasing knowledge and experience in the use of these preparations.

The majority of articles have been concerned with the efficacy of protamine zinc insulin after it had been shown to have a more prolonged effect than protamine insulin. Much less has been written concerning the use of crystalline insulin; this has been summarized in a recent report by Altshuler.[6] The consensus has been that the prolonged hypoglycemic action of crystalline insulin was attributable to its zinc content and that its sphere of prolonged action lay somewhere between that of protamine zinc insulin and regular insulin. Altshuler and Leiser [7] have shown recently, however, that the prolonged action of crystalline insulin cannot be attributed entirely to its zinc content.

Because our results with protamine zinc insulin agree in general with those reported from other clinics it is not our purpose to encumber the numerous list of articles with additional supporting evidence. The advent of crystalline insulin, however, has provided an opportunity to compare its efficacy with that of protamine zinc insulin in a group of ambulatory patients

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with uncomplicated diabetes in the Out-Patient Department of the University of California Medical Center. Because our clinical experiences with crystalline insulin have been more favorable than one might expect from some of the previous reports, it is felt their presentation in this paper is warranted.

During the past 18 months we have studied the effect of protamine zinc insulin and crystalline insulin * in a group of 52 ambulatory patients chosen at random in the Diabetic Clinic of the University of California Out-Patient Department. There were 37 females and 15 males; the average age of the whole group was 41 years with extremes of 13 to 69 years. The average known duration of diabetes was six years, the extremes being 1 to 17 years.

The patients were grouped arbitrarily according to the severity of their diabetes as follows: Mild diabetics were those controlled on 25 units or less of regular insulin daily; those requiring from 25 to 50 units daily were classified as moderately severe, and those receiving 50 units or more daily were considered as severe.

The degree of control of diabetes in this study was determined by frequent analyses of the urine fractions brought to the Clinic by the patient. The fractional method of urine examination is well known and is employed in many diabetic clinics. Briefly, the method constitutes the collection of four specimens of urine by the patient over a period of 24 hours prior to the visit to the clinic in the following manner:

The patient is directed to collect all the urine voided from breakfast to lunch in one container on the day preceding the visit to the diabetic clinic. A small sample of urine from this bottle is labeled specimen 1 and brought to the Clinic together with samples of urine similarly collected from lunch to supper (specimen 2), supper to bedtime (specimen 3) and from bedtime to breakfast (specimen 4) on the morning of the visit to the clinic. The samples are then tested for glucose by the Benedict qualitative method.

A classification of the degree of control of diabetes was chosen arbitrarily using the following criteria:

1. Patients whose urines were consistently negative (no reduction) using Benedict's qualitative test for the presence of glucose, or which showed only occasionally a "green" reduction were considered as well controlled.
2. Patients whose urines showed an average "green" to "yellow" reduction were considered as moderately well-controlled.
3. Patients whose urines consistently showed an average "yellow" to "orange" reduction were considered as uncontrolled.

This routine was employed both before and after the substitution of protamine zinc insulin or crystalline insulin for regular insulin. Examinations of the urines were made twice weekly following the administration of

* The protamine zinc insulin used in this study was supplied by Eli Lilly & Co. and E. R. Squibb & Sons. Crystalline insulin was supplied by the Frederick Stearns Co.

long-acting insulins until the patients were satisfactorily controlled, then once a week. The average duration of observation of the patients in this group on regular insulin was 29.8 months; the average duration of observation for the same group following the administration of protamine zinc insulin and of crystalline insulin was 7.3 months.

The purely clinical nature of this study and the ambulatory status of the patients, most of whom were employed, and many on relief made frequent blood-sugar determinations impracticable.

It should be emphasized that the dietary regime remained unchanged following the substitution of protamine zinc insulin or crystalline insulin for regular insulin. In our hands the most satisfactory diet has been one with a moderately high carbohydrate content, 150 to 160 grams daily; the daily protein requirement being fulfilled with one gram of protein per kilo body weight. Fats were allowed in amounts necessary to maintain a constant body weight.

Because the majority of the patients studied were employed, and many were on relief, it soon became apparent that the transition from regular insulin to protamine zinc insulin or crystalline insulin would have to be accomplished with a minimal expense and change in the patient's daily routine. Accordingly, the following procedure using either protamine zinc insulin or crystalline insulin was carried out.

1. In substituting long-acting insulin for regular insulin in the treatment of patients with mild diabetes, requiring two doses of regular insulin daily, we usually employed a total daily dosage of the long-acting insulin which was 5 or 10 units less than the amount of regular insulin previously required, and prescribed a single injection in the morning three-quarters of an hour before breakfast.

2. In patients with a moderately severe diabetes receiving three injections of regular insulin daily, we attempted to reduce the number of injections of long-acting insulin to two. At the same time an attempt was made either to maintain the same total dosage or, if possible, to reduce it by 5 to 10 units. If these patients continued to be aglycosuric for several weeks the total daily dosage (units per day) was reduced to a figure consistent with satisfactory control. Among patients in this group who had been receiving only two injections of regular insulin daily an attempt was made to regulate them with only one injection of long-acting insulin and moreover with a lesser number of units per day.

3. In patients with severe diabetes, who received two or more injections of regular insulin daily, the procedure as described above for patients with a moderate diabetes, was followed. In this group, we found protamine zinc insulin U–80 to have the same effect, unit for unit, as the U–40 preparation. The advantage of U–80 protamine zinc insulin in patients receiving more than 40 units at a single injection is obvious.

4. Early in our studies we were influenced by numerous reports, that

the postprandial hyperglycemia, so likely to occur after breakfast using only one dose of protamine zinc insulin in the morning daily, made it advisable to accompany the morning dose of protamine zinc insulin with a small dose of regular insulin. This procedure was carried out in 13 of the patients included in this study.

TABLE I

Per cent reduction both in dosage (units of insulin per day) and number of daily injections following substitution of long-acting insulins for regular insulin in 52 patients.

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction Average Total Daily Dosage	35%	13%	15%
Reduction Average Number Daily Injections	46%	44%	16%
Number of Cases	16	23	13

Table 1 shows the results of the previously outlined study in 52 diabetic patients, all of whom had been treated with regular insulin. Sixteen were transferred to crystalline insulin, 23 to protamine zinc insulin and 13 to protamine zinc insulin and regular insulin together. The most outstanding results were obtained with crystalline insulin. The average total daily dosage of crystalline insulin was smaller by 35 per cent than the former regular insulin dosage. Using the protamine zinc insulin alone or in combination with regular insulin, the reduction in dosage was only 13 per cent and 15 per cent respectively. The number of injections, when both protamine zinc insulin and regular insulin were employed, was only reduced by 16 per cent from the number formerly required with regular insulin. This was to be expected since the minimum number of injections using both types of insulin must be two.

Better control of diabetes followed the use of both crystalline and protamine zinc insulin as compared to regular insulin. Table 2 shows, how-

TABLE II

Degree of Control of Diabetes in 52 Patients Before and After the Administration of Long-Acting Insulin.

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not Controlled	44%	0	17%	9%	30%	23%
Fair Control	18%	18%	17%	17%	30%	8%
Well Controlled	38%	82%	66%	74%	40%	69%
Number of Cases	16	16	23	23	13	13

ever, that the greatest percentage of controlled cases were those changed from regular to crystalline insulin. Whereas 44 per cent of the patients,

who later received crystalline insulin, were not controlled on regular insulin, none were uncontrolled after its administration; the percentage of well controlled cases was correspondingly increased from 38 per cent to 82 per cent. Less striking results were noted with protamine zinc insulin alone or in combination with regular insulin.

Of the 52 patients studied, 19 had severe diabetes according to the criteria outlined previously, 23 were considered as having moderately severe diabetes and 10 had mild diabetes. In order to determine the efficacy of the long-acting insulins in these three types of cases, our data were analyzed separately for each group. The results of this analysis are compiled in tables 3, 4, 5, 6 and 7.

TABLE III

Reduction in Insulin Dosage and Number of Daily Injections Following Substitution of Long-Acting Insulin for Regular Insulin in 19 Patients with *Severe* Diabetes.

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction average total daily dosage	48%	22%	4%
Reduction average number daily injections	41%	43%	28%
Number of cases	5	8	6

TABLE IV

Degree of Control of Diabetes in 19 Patients with *Severe* Diabetes before and after the Administration of Long-Acting Insulin.

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not controlled	60%	0	25%	25%	50%	33%
Fair control	40%	20%	25%	25%	33%	0
Well controlled	0	80%	50%	50%	17%	67%
Number of cases	5	5	8	8	6	6

TABLE V

Change in Daily Dosage and Number of Daily Injections of Insulin Following Substitution of Long-Acting Insulin for Regular Insulin in 23 Patients with *Moderately Severe* Diabetes.

	Crystalline Insulin	Protamine Zinc Insulin	Protamine Zinc Insulin and Regular Insulin
Reduction average daily dosage	23%	4% increase	9%
Reduction average number daily injections	59%	40%	5%
Number of cases	6	10	7

TABLE VI

Degree of Control of Diabetes before and after the Use of Long-Acting Insulin in 23 Patients with *Moderately Severe* Diabetes.

	Regular Insulin	Crystalline Insulin	Regular Insulin	Protamine Zinc Insulin	Regular Insulin	Protamine Zinc Insulin and Regular Insulin
Not controlled	17%	0	20%	0	15%	15%
Fair control	17%	17%	20%	20%	28%	15%
Well controlled	66%	83%	60%	80%	57%	70%
Number of cases	6	6	10	10	7	7

TABLE VII

Reduction in Dosage, Number of Daily Injections and Degree of Control in 10 Patients with *Mild* Diabetes before and after the Use of Long-Acting Insulin.

	Regular Insulin	Crystalline Insulin	% Reduction	Regular Insulin	Protamine Zinc Insulin	% Reduction
Average daily dose	18	17	6%	19.8	17.0	9%
Average number injections daily	2.2	1.6	27%	2	1	50%
Cases uncontrolled	3	0		0	0	
Fair control	0	1		0	0	
Well controlled	2	4		5	5	
Number of cases	5	5		5	5	

The greatest reduction in total daily dosage of insulin (units per day) occurred in the *severe* and *moderately severe* diabetics following the use of crystalline insulin (tables 3 and 5). The average daily dose of insulin in the mild diabetics (table 7) was reduced very little following the use of protamine zinc insulin or crystalline insulin. In this group there was a slightly greater reduction in insulin dosage with protamine zinc insulin. It is of interest to note that following the use of protamine zinc insulin, in the moderately severe diabetics, there was a 4 per cent increase in dosage over the amount of regular insulin previously administered.

The greatest reduction in the number of injections daily occurred in the moderately severe diabetics following the use of crystalline insulin (table 5). The number of injections per day in this group was found to be reduced over 50 per cent as compared to a 40 per cent reduction following the use of protamine zinc insulin, and a 5 per cent reduction using protamine zinc insulin and regular insulin combined. In the mild diabetics a greater reduction in the number of injections daily followed the use of protamine zinc insulin (table 7) and in the severe diabetics the reduction in injections (table 3) was about the same following the use of crystalline and protamine zinc insulin.

An analysis of tables 4, 6 and 7 shows that those diabetics transferred to crystalline insulin were better controlled than those on protamine zinc insulin alone or in combination with regular insulin. This finding was most apparent in the severe diabetics (table 4). In this group the well-controlled cases were increased 80 per cent following the use of crystalline insulin; improvement in control of the mild and moderately severe diabetics was less striking.

It is quite apparent that the use of crystalline insulin in this study has resulted in a reduction not only in the number of injections of insulin daily and the number of units administered per day in the majority of cases, but has improved remarkably the control of the diabetes in all. Similar results were obtained with protamine zinc insulin alone or in combination with regular insulin but to a less striking degree.

While our results with crystalline insulin were entirely unexpected at the time, others have apparently had similar experiences with this preparation. Allen [8] has found that in the most severe and labile diabetic patients the original hope that protamine zinc insulin would facilitate control of hyperglycemia has not been fulfilled. He has found that crystalline insulin in such cases proved distinctly helpful, despite the fact that its duration of prolonged action was not equal to that of protamine zinc insulin. Our clinical experiences in this work indicate that better results are to be expected with long-acting insulins in the severe and moderately severe diabetics. Patients whose daily insulin requirements are small may be satisfactorily controlled on regular insulin, although the number of injections per day may often be reduced with long-acting insulin. Diabetic patients who are not faithful to dietary limitations, or who are insulin sensitive or resistant, present as great a problem under the administration of insulins with prolonged action as they do with regular insulin. The variability in response to therapy and in coöperation of the patients in this study undoubtedly have had a bearing on these results; for these reasons further studies are desirable. It would seem reasonable to assume, however, that crystalline insulin has a definite place in the treatment of certain diabetics, where the longer action of protamine zinc insulin and its greater accumulative effect may not be altogether desirable.

Summary and Conclusions

A group of 52 patients with uncomplicated diabetes previously treated with regular insulin were transferred to protamine zinc insulin and crystalline insulin therapy. These patients were chosen at random and classified as having severe, moderately severe or mild diabetes.

After satisfactory periods of observation under regular insulin therapy and with the insulins of prolonged hypoglycemic activity, we found that this particular group of patients, analyzed as a whole, showed a definite reduction in the average total daily dosage, after the change over to long-

acting insulins. This reduction was greatest among those patients transferred to crystalline insulin. A definite reduction in the average number of daily injections likewise followed the use of long-acting insulins and this was about the same for those patients who received protamine zinc insulin alone and crystalline insulin. Better control of diabetes followed the use of the long-acting insulins. This was most outstanding among the patients who received crystalline insulin.

An analysis of our results with the different types of insulins in patients with diabetes of varying degrees of severity showed that a greater reduction in the total daily insulin dosage followed the use of crystalline insulin in patients with severe and moderately severe diabetes. Among a smaller group of mild diabetics the reduction in dosage was not great and was about the same for crystalline and protamine zinc insulin.

Among the patients with moderately severe diabetes the greatest reduction in the number of injections per day followed the use of crystalline insulin. The reduction in daily injections in the severe diabetics was approximately the same following the crystalline and protamine zinc insulin, whereas in a small group of mild diabetics this reduction was greater following protamine zinc insulin.

Improvement in the control of diabetes was most outstanding in patients with severe diabetes after they had been changed over to crystalline insulin.

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THE PRESSOR RESPONSE OF NORMAL AND HYPERTENSIVE HUMAN SUBJECTS TO TYRAMINE INTRODUCED INTO THE ILEUM *

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THE recent experiments of Goldblatt and his collaborators have shown that hypertension follows the production of renal ischemia in the dog. The facts that its development is entirely independent of the renal [1] or sympathetic nerves [2] and that its maintenance depends on the presence in the body of ischemic renal tissue [3] suggest that the hypertension so produced is due to a circulating pressor substance. This view is strengthened by the demonstration that kidneys of animals rendered hypertensive by experimental renal ischemia yield on extraction pressor substances in greater amount than do normal kidneys.[4, 5] These observations have stimulated the search both for factors causing primary renal ischemia in man, and for a pressor agent which might be identified consistently in the hypertensive state. Tyramine (para-hydroxy-phenyl-ethylamine), a known vasoconstrictor substance, has been implicated in both respects.

Evidence exists which suggests that tyramine is a pressor agent resulting from renal ischemia, since it has been found in the blood of experimental animals rendered hypertensive by partial occlusion of the renal arteries [6]; on the other hand, recent experiments [7] have demonstrated that it may be the cause of renal ischemia, for its parenteral introduction into experimental animals for the period of a year resulted in arteriolar nephrosclerosis similar to that observed in the kidneys of hypertensive subjects.

Tyramine taken by mouth in usual doses is totally inactive, but when it was introduced directly into the ileum by means of intestinal intubation we observed a transient but definite rise in blood pressure. This observation made it seem reasonable to reopen the question of whether certain individuals develop primary renal ischemia and secondary hypertension because they lack the normal protection against prolonged exposure to the vasoconstrictor effects of tyramine absorbed from the lower intestinal tract, where bacteria normally present are capable of forming it from tyrosine.[8] Such a lack of protection in hypertensive subjects should make them unusually susceptible to the effects of tyramine. In searching for such susceptibility we have compared the pressor response of normal and hypertensive subjects to the introduction of tyramine into the ileum. The results

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lead us to the conclusion that no significant difference exists between the two groups.

Methods

The subjects were divided into two groups: 13 with normal blood pressure and no significant evidence of cardio-vascular, renal or digestive disease, and 13 with hypertension, 6 of the latter having benign or essential hypertension and 7, malignant hypertension. The subjects, who had fasted

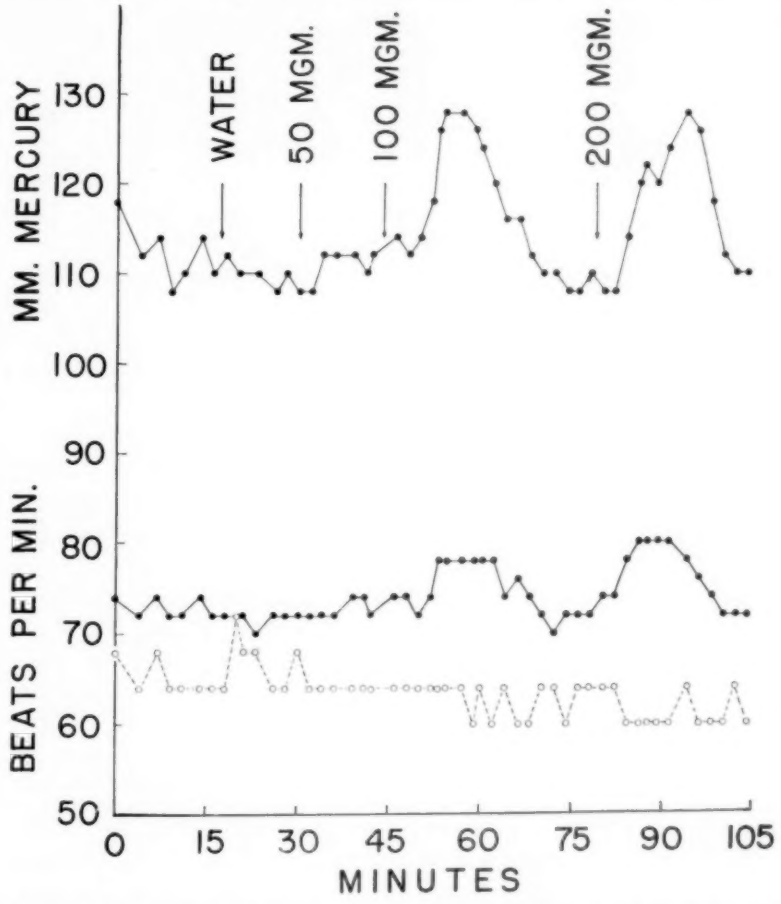

Fig. 1. The effect on pulse and blood pressure of ascending doses of tyramine introduced into the ileum of a normal human subject. The open circles indicate pulse rate.

for approximately 16 hours, were intubated by the method of Miller and Abbott.[9] A double-lumened tube was introduced, with fluoroscopic guidance, into the duodenum. A small balloon connected with the distal end of one lumen was then inflated with air, and the tube was allowed to progress until its tip was found by fluoroscopic observation to be in the ileum, when further progress was stopped by deflating the balloon. With the sub-

ject lying at rest frequent readings of pulse and of systolic and diastolic blood pressure were made with a clinical mercury manometer. When the readings were reasonably constant 15 c.c. of water were introduced through the open lumen of the tube, and its effects on pulse and blood pressure were observed. This control measure was necessary since the subjects were all made aware of the introduction of solutions by a sensation of coolness in the throat. Fifty, 100 and 200 mg. of tyramine hydrochloride in 15 c.c. of water were introduced serially, and the responses determined. The exact portion of the ileum into which the tyramine was introduced varied in the different subjects without apparent influence on the results.

Results

The response of a typical normal subject is observed in figure 1. The introduction of water alone produced no detectable effect on the blood pressure and only a slight, temporary increase in the pulse rate. Fifty mg. of tyramine were followed by no change whatever, while 100 mg. caused the systolic blood pressure to rise approximately 20 mm. of Hg and the diastolic only 5 mm. of Hg above the resting level. The pulse rate was somewhat slower during the rise in blood pressure. Two hundred mg. of tyramine produced an effect essentially similar to that of 100 mg., which is exceptional in that the height of the blood pressure rise was ordinarily proportional to the size of the dose. The blood pressure curve was at its highest point in 12 to 15 minutes and returned to normal in 20 to 25 minutes after the drug was administered. Taking the results as a whole, the blood pressure change was chiefly in the systolic reading; diastolic pressure was either unchanged or very slightly increased. The pulse was usually somewhat slowed or was unchanged. Pallor of the skin was not observed. Subjective symptoms were rare: a few subjects noticed transient palpitation at the height of the blood pressure elevation, but as a rule they had no unusual sensations.

Table I

A comparison of reactivity of normal and hypertensive subjects to tyramine. A rise in systolic blood pressure of 10 mm. of Hg or more was regarded as a positive response.

	50 Mg.		100 Mg.		200 Mg.	
	Normal	Hyper.	Normal	Hyper.	Normal	Hyper.
Reactive	1	5	5	8	8	2
Non-reactive	12	6	8	3	2	2
Percentage of positive reactors	7%	45%	38%	72%	80%	100%

Table 1 compares the percentage of subjects from both groups regarded as having a significant rise in blood pressure following tyramine. An elevation in the systolic pressure of 10 mm. of mercury or more above the rest-

ing level was taken as evidence of drug action since the spontaneous variations during the control period were always distinctly less than this. The average dose per kilogram of body weight was identical in the two groups, 0.8 and 1.6 mg. per kilo for the 50 and 100 mg. doses respectively. This was also the average dose of the positive reactors in the hypertensive group. It will be observed that the percentage of positive reactors in the latter group was consistently greater, whatever the dose of tyramine. Perhaps a more accurate picture of the observed difference is obtained from comparison in the two groups of the actual curves of systolic blood pressure following the administration of 50 and 100 mg. of tyramine (figure 2). Although an

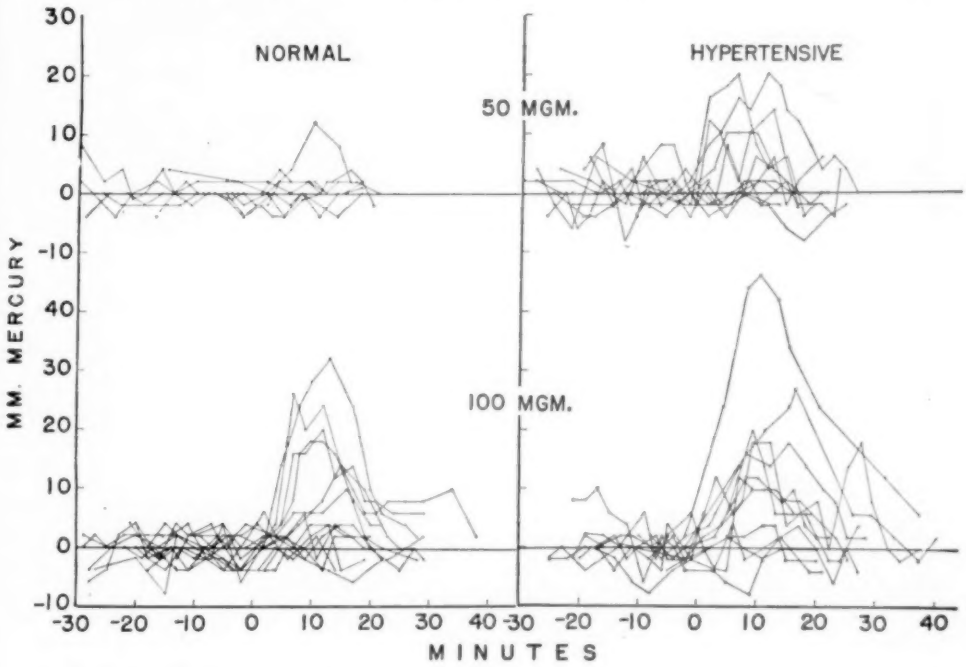

FIG. 2. Comparison of the response of normal and hypertensive subjects to the introduction of 50 and 100 mg. tyramine into the ileum.

obvious difference between the curves is apparent, it will be noted that the time of onset, magnitude and duration of the elevation of blood pressure were much alike. Changes in the diastolic pressure and pulse rate and incidence of subjective symptoms did not differ materially. Thus the character of the response, when it occurred, was more or less fixed, and the chief difference lay in its higher incidence in the hypertensive group.

DISCUSSION

It is conceivable that the inherent defect which ultimately leads to the development of clinical hypertension in susceptible individuals consists in

some abnormality which permits prolonged exposure of the organism to the vasoconstrictor effects of tyramine. Such abnormality might reside either in the intestinal wall, allowing absorption of abnormally large amounts of the substance, in the liver, which normally destroys tyramine reaching it through the portal circulation,[10] or in the peripheral vasomotor apparatus which might be unusually sensitive to its action. If such were the case it seems reasonable to expect that this defect should be disclosed either by an abnormally great or by an excessively prolonged pressor response following introduction of this substance into the lower intestine. Unfortunately absolute criteria of what constitutes a normal response do not exist, hence the interpretation of the results must be a matter of opinion. The present experiments have disclosed that certain of the hypertensive subjects did, indeed, react to tyramine with an elevation of blood pressure distinctly higher, and in some cases, more prolonged than that in the normal subjects. However, for two reasons we do not believe that our data necessarily provide evidence that the concept outlined above is correct. First, it will be observed that some of the hypertensive subjects were totally unreactive to tyramine, others gave normal responses, still others were hyper-reactive. In other words a marked individual variation in susceptibility was demonstrated. This same variability was observed in the normal subjects. If sensitivity to tyramine constituted a fundamental etiologic factor in hypertension it should have manifested itself, in our opinion, with much greater uniformity than was the case. In the second place, it is well recognized that a variety of unrelated stimuli such as cold,[11] pain,[12] exercise,[13] injection of adrenalin[14] and inhalation of CO_2[15] produce abnormally great elevation of blood pressure in hypertensive individuals. The nature of this hyper-reactivity is the subject of discussion,[16] but whatever the cause the variety of stimuli which produce it make one cautious in attributing special significance to tyramine and suggest that the heightened response to this substance in the hypertensive group is an expression of a general, non-specific hyper-reactivity.

Two earlier observations with respect to tyramine in hypertension deserve comment here, since though unrelated to the present experiments they bear on the general problem at hand. Reference has been made to the fact that tyramine administered to experimental animals daily for the period of a year produced nephrosclerosis.[7] Though extensive vascular and parenchymal changes were present in the kidneys of two dogs so treated, neither developed hypertension. This observation, if substantiated by more extensive data, raises serious question whether the arteriolar nephrosclerosis caused by prolonged tyramine administration is capable of producing permanent hypertension in the same fashion as the more acute reduction of renal blood supply employed experimentally by Goldblatt.

Recent experiments of Landis, Montgomery and Sparkman[17] have provided important data relating to the hypertensive action of tyramine, which raise further doubt as to the importance of its rôle in human hypertension.

In studying the effects of a variety of agents on the blood pressure and peripheral blood flow of the unanesthetized rabbit they found certain differences in the circulatory dynamics which appear to be of fundamental importance. All of the pressor drugs studied, including tyramine, produced a rise in blood pressure and with it a definite decrease in the peripheral blood flow. Heated saline extracts of rabbit kidney, on the other hand, produced hypertension without evidence of decreased peripheral blood flow. This is precisely the condition found in human hypertension,[18] and the fact that the hypertension produced by tyramine differs from it in such a fundamental respect further weakens, in our opinion, the belief that tyramine is concerned in the development of human hypertension.

Summary

Tyramine, introduced into the ileum of human subjects by means of small intestinal intubation, produced a transient but unequivocal rise in blood pressure. The response to this substance has been compared in normal and hypertensive subjects. The hypertensive group was slightly more reactive than normal, i.e. the percentage of those having a significant rise in blood pressure was greater, and the pressor response was in general somewhat higher, although its duration was similar. The results are interpreted as further evidence of the lability of blood pressure in hypertensive individuals. The observed difference in response was not considered sufficiently striking to suggest that one of the factors in the etiology of hypertension is a constitutional susceptibility to the effects of tyramine.

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CEREBROVASCULAR COMPLICATIONS IN THROMBO-ANGIITIS OBLITERANS *

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It is now known that thrombo-angiitis is a disease which is not limited to the extremities. In the recent literature much stress has been laid upon the fact that the vascular lesions associated with thrombo-angiitis obliterans frequently involve the coronary arteries, or that the disease of the coronary arteries is frequently associated with thrombo-angiitis. It is the purpose of this paper to emphasize another complication of thrombo-angiitis obliterans, namely, involvement of the cerebral vessels.

We have been able to find in the literature 23 cases in which involvement of the cerebral arteries was associated with thrombo-angiitis obliterans of the extremities. These include four cases reported by Averbuck and Silbert [1] (cases 37, 42, 46 and 47), three cases reported by Jäger [2] (cases 2, 3, and 4), two cases reported by Linenthal and Barron [3] and two by Foerster and Guttmann [4] (cases 1 and 2), and one case each reported by Essen,[5] Lewis,[6] Gresser,[7] Spatz,[8] Livingston,[9] Merkelbach,[10] Bauer and Recht,[11] Stahnke,[12] Kerr and Underwood,[13] Friedmann,[14] López Albo,[15] and Buerger.[16] In addition, Dr. Teresa McGovern of New York City has kindly sent us the records of a patient with thrombo-angiitis obliterans who also had marked contraction of the visual fields. While these cases which have been reported may be cases of characteristic thrombo-angiitis obliterans, such a diagnosis could not be made certainly from the reports by Essen, Gresser, Jäger (case 4), Averbuck and Silbert (case 47), and López Albo because of the presence of diabetes or hypertension, or because the patient was older than most of those with thrombo-angiitis obliterans, or because the clinical reports were insufficient.

The diagnosis of thrombo-angiitis obliterans involving the peripheral arteries seems reasonably certain from the reports of cases by Linenthal and Barron, Foerster and Guttmann, Merkelbach, Bauer and Recht, Averbuck and Silbert (cases 37 and 42), Friedmann, and Buerger although pathologic studies of the cerebral lesions were not reported. The case of Kerr and Underwood was not reported as being one of thrombo-angiitis obliterans with cerebral involvement but as an example of vascular constriction associated with a lesion of the brain. However, we have included it as it may possibly be an example of thrombo-angiitis obliterans. In Jäger's case 4 there was no report suggesting disease involving the peripheral arteries. However, on pathologic examination the arteries of the lower extremities

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were thrombosed. On microscopic examination of the cerebral and peripheral arteries evidence of degeneration and inflammation was found. In the cases reported by Lewis, Spatz, Jäger (cases 2 and 3), Livingston, Stahnke, Averbuck and Silbert (case 41), either the clinical history or the organic changes indicated thrombo-angiitis obliterans of the peripheral arteries and pathologic studies of the cerebral vessels were made. In the case reported by Lewis, the nature of the intracranial lesion was not reported. In Stahnke's case there was apparently embolism. In Jäger's cases 2 and 3, both inflammation and degeneration were found in the cerebral vessels, and in Averbuck and Silbert's cases 46 and 47, the lesions were apparently entirely sclerotic. Good examples of thrombo-angiitis obliterans involving the peripheral and cerebral vessels will be found in Spatz and Livingston's cases.

While the clinical symptoms of cerebral involvement reported by the foregoing authors varied, they did have some common characteristics. Transient neurologic changes, such as hemianopia (reported by Foerster and Guttmann in case 2, Spatz, and Merkelbach), or hemiplegia, which was either transitory or constant or occurred repeatedly (Linenthal and Barron's cases 1 and 2), Lewis, Spatz, Jäger (cases 2 and 3), Livingston, Bauer and Recht, Averbuck and Silbert (cases 37, 42 and 46) were noted.

We concluded from a study of the cases reported that patients who have clinical cerebral manifestations of thrombo-angiitis obliterans may have cerebral lesions on a different pathologic basis. Since the clinical evidence of cerebral involvement may be the same in these cases, it is impossible to predict the nature of the cerebrovascular lesion when there is clinical evidence of such lesions, as they may be inflammatory, that is, characteristic of thrombo-angiitis obliterans, or degenerative, that is, characteristic of arteriosclerosis, or they may represent a combination of these two processes. The finding of sclerotic changes in the cerebral vessels in cases of thrombo-angiitis obliterans is in keeping with observations made previously that, in cases of involvement of the coronary arteries in this condition, the pathologic changes are almost uniformly arteriosclerotic in origin (Saphir). The important observation arrived at from study of reports mentioned in the preceding paragraphs is that lesions of the cerebral vessels, while not always characteristic of thrombo-angiitis obliterans, may affect individuals with this disease of the extremities who do not have syphilis, hypertension, or diabetes, or other detectable causes for cerebrovascular lesions.

At The Mayo Clinic we have observed 11 patients with thrombo-angiitis obliterans involving the extremities who had evidence of vascular lesions involving the brain. Brief reports of these cases follow:

Report of Eleven Cases Observed at The Mayo Clinic

Case 1. A man, 50 years old, was admitted to the clinic in September 1932. He had smoked from 20 to 40 cigarettes a day. He had had superficial phlebitis recurrently, and three years previously headaches and vomiting had been followed by

a defect in vision. Two years prior to admission he had noticed cramps in his right arm, and coldness and cyanosis of his right hand and fingers. These symptoms had become progressively worse. A year and a half prior to examination intermittent claudication affected his left leg. About six months before this he had fainted but had revived within a few minutes; there was no residual paralysis. Six months prior to examination he became faint and there was numbness of the right side of his face and of his hands and he had an impairment of speech. These symptoms, however, disappeared quickly. At the time of examination pulsations were absent in the left femoral and popliteal arteries and in the posterior tibial and dorsalis pedis arteries bilaterally. Neurologic examination gave essentially negative results except for left homonymous hemianopia. The blood pressure in the left brachial artery was 110 systolic and 68 diastolic. The patient then left the hospital against advice and returned one month later, four days after sudden occlusion of the right femoral artery. The findings were essentially as before except that pulsations were absent in the right popliteal artery and there was marked cyanosis of the right first, second and third toes. The right leg was amputated in November 1932, and examination of its vessels showed changes characteristic of thrombo-angiitis obliterans. Left lumbar sympathectomy was performed in February 1933, at which time thrombosis of the left common iliac and internal iliac arteries and veins was found; there was marked perivascular inflammation. In July 1933, the left leg was amputated. A letter from the patient's physician stated that he had died of symptoms of myocardial infarction in September 1933.

Case 2. A man, 42 years old, was admitted to the clinic in October 1932. He had smoked 10 cigarettes a day since the age of thirteen. Eight and three years respectively, prior to examination he had had superficial phlebitis affecting his left calf and for a year prior to examination he had had intermittent claudication affecting his left calf and arch. At the time of examination pulsations were absent in the left dorsalis pedis and posterior tibial arteries and were markedly diminished in the right posterior tibial and dorsalis pedis arteries. There was an abnormal amount of pallor on elevation of the left foot and abnormal rubor on dependency. The blood pressure was 132 systolic and 86 diastolic. Bilateral lumbar sympathectomy was performed in October 1932. On the seventh day following operation it was discovered that the patient was unable to move his right arm and leg and that he was unable to talk. At the time of examination there was evidence of right hemiplegia. He returned to the clinic in April 1933, at which time there was evidence of improvement; the hemiplegia, however, was again present when he was reëxamined in August 1936. There was no evidence of progression of the arterial lesions, although the patient subsequently had superficial phlebitis.

Case 3. A man, 37 years old, was examined at the clinic in March 1930. He had smoked 20 cigarettes a day for many years. For three years he had had claudication involving the left leg. He gave a history suggestive of recurrent phlebitis involving the legs and arms for the previous two years. For one year there had been ulceration of the toes of the left foot and fatigue in the right hand when writing. Six months prior to examination an ulcer had developed on the right index finger, and two weeks prior to admission to the hospital the left second toe had been amputated. Examination showed occlusion of the radial, ulnar, posterior tibial, and dorsalis pedis arteries, bilaterally, and of the left popliteal artery; pulsations were diminished in the femoral artery, bilaterally, and in the right popliteal artery. There was a gangrenous wound where the left second toe had been amputated previously. The blood pressure was 130 systolic and 86 diastolic. One year after examination at the clinic, left hemiplegia occurred from which recovery was complete in several weeks. This was followed by another episode of hemiplegia from which the patient recovered only very slowly.

Case 4. A man, 39 years old, was examined at the clinic in September 1930.

He had had intermittent claudication involving the legs for six months. Superficial phlebitis had been absent. On examination pulsations were found to be absent in the posterior tibial and dorsalis pedis arteries, bilaterally. The blood pressure was 94 systolic and 60 diastolic. One year after dismissal from the clinic we were informed by letter that he had had hemiplegia involving the left side.

Case 5. A man, 47 years old, was examined at the clinic in February 1935. Two years previously he had sustained left hemiplegia, from which he gradually recovered. He had passed a life insurance examination at the age of 42, but at the time the hemiplegia occurred the blood pressure was said to have been 210 systolic. One year prior to admission to the clinic he had noted bilateral claudication in his arches and calves; about seven months later trophic changes developed in the toes of the right foot and the toe nails had to be removed. On examination at the clinic pulsations were absent in the posterior tibial, dorsalis pedis, and popliteal arteries bilaterally. Gangrene of the distal part of the right first toe and two areas of superficial phlebitis below the right knee were present. The blood pressure on several occasions was found to range between 140 and 95 systolic and 85 and 60 diastolic. There was a residual facial weakness, awkwardness and slowness of the left hand, increased deep reflexes of the left arm, positive Hoffman's sign on the left, and a questionable positive Babinski on the left. Amputation of the left leg was performed February 21, 1935. Examination of the vessels of the amputated extremity showed changes characteristic of thrombo-angiitis obliterans. A short time after leaving the clinic the patient died suddenly with what was said to have been evidence of a cerebrovascular accident.

Case 6. A man, 35 years old, was examined at the clinic in July 1929. He had had symptoms of vascular disease involving his lower extremities for five years and pains in the fingers of his left hand for three years. He had also had three severe attacks of pain in the left pectoral region, without projection but associated with dyspnea, the longest attack having lasted 20 minutes. Following this the pain had recurred on exertion, and especially in cold weather; it was relieved by nitroglycerin and rest. He had had a primary syphilitic infection in 1924. On examination at the clinic there was marked impairment of pulsations in the dorsalis pedis and posterior tibial arteries bilaterally, and in the left dorsalis pedis artery; marked blanching on elevation of the right foot, and less so on the left, and a moderate degree of abnormal rubor when the feet were dependent were noted. Trophic changes involved the nails of both feet. The blood pressure was 155 systolic and 90 diastolic. The flocculation test on the blood was positive but that on the spinal fluid was negative. The spinal fluid contained two cells per cubic millimeter. Diagnoses of thrombo-angiitis obliterans, angina pectoris, and latent syphilis were made. Two years after leaving the clinic we were informed that the patient had sustained a cerebrovascular accident with impairment of speech.

Case 7. A man, 39 years old, was examined at the clinic in September 1930. At the age of 36 he had sustained a right hemiplegia from which he recovered in three weeks. He had known of the existence of hypertension for only six months prior to his examination at the clinic. Eighteen months after the hemiplegia, intermittent claudication of the right leg had developed and intermittent claudication had subsequently affected the left leg also. At the time of examination the blood pressure ranged from 140 to 220 systolic and from 80 to 128 diastolic. Examination of the ocular fundi showed arteriosclerosis, grade 1. Pulsations were absent in the popliteal and dorsalis pedis arteries, bilaterally, and in the left femoral and posterior tibial arteries; they were impaired in the right radial artery. There was abnormal pallor with elevation of the left foot. There was no evidence of hemiplegia. A serologic test for syphilis was negative.

Case 8. A man, 43 years old, was examined at the clinic in June 1932. At the age of 29 years he noticed weakness involving his right arm, which in one tc

two hours had progressed until right hemiplegia was complete. The right side of his face was paralyzed and aphasia was present. This paresis persisted for two months and then gradually improved. At the age of 42 he noted intermittent claudication involving his left calf and shortly thereafter rest pain in his left foot, which necessitated amputation of the leg. Pulsations were absent in the right popliteal, posterior tibial, and dorsalis pedis arteries and in the left ulnar artery. There was marked abnormal pallor and rubor of the right leg on dependency and elevation. The flocculation test for syphilis on both blood and spinal fluid was negative. Neurologic examination showed evidence of a residue of a right hemiplegia. The blood pressure was 134 systolic and 88 diastolic.

Case 9. A man, 49 years old, was first examined at the clinic in July 1931. He had had intermittent claudication involving the right calf for four months and superficial phlebitis about three months before admission. His blood pressure was 190 systolic and 110 diastolic. At the time of examination pulsations were absent in the right popliteal, posterior tibial, and dorsalis pedis arteries. Examination of the ocular fundi showed mild narrowing of the retinal arteries. A serologic test for syphilis was negative. The patient was re-admitted to the clinic in January 1932, at which time he had symptoms of duodenal ulcer. The condition of the vascular disease was unchanged. The patient was again examined at the clinic in May 1933, because of more difficulty with the ulcer, and at that time posterior gastroenterostomy was performed for chronic duodenal ulcer with obstruction. His blood pressure was 120 systolic and 70 diastolic. The patient again returned to the clinic in September 1933, stating that five weeks previously he had noted numbness and weakness in his left hand and in his face and that ten days before admission he had twitching involving his left hand and leg; this, however, had disappeared in a short time. He was again reëxamined at the clinic in June 1934, at which time he stated that six weeks previously, during excitement, he had become dazed and had got into his car and apparently bumped into some other cars while trying to get out of a parking space. He did not remember much about the drive home. After a day or so the confusion cleared somewhat but he still had some difficulty with his speech. His local physician reported that he had been unconscious for about 24 hours. He was in the hospital for a time and, on one occasion, felt twitching in the left side of his face. His wife said that he forgot easily and repeated frequently. Superficial phlebitis had occurred. Neurologic examination at the clinic gave essentially negative results. The blood pressure varied between 145 and 128 systolic and was 70 diastolic. Examination of the ocular fundi showed normal retinal vessels. The popliteal, posterior tibial, and dorsalis pedis arteries were occluded bilaterally. On April 27, 1934, the patient had an attack with slight paralysis of the face and arm which lasted but a few days. He then got along splendidly after this episode except that his mental confusion did not disappear. On May 12 he had another attack, somewhat slighter than the first. The paralysis again cleared up but mentally the patient became more confused than before.

Case 10. A Jew, 59 years old, was examined at the clinic in May 1929. He had had intermittent claudication since the age of 45 and several severe attacks of superficial phlebitis. At the time of examination the dorsalis pedis, posterior tibial, and popliteal arteries were occluded bilaterally, and the pulsations were diminished in both femoral arteries and absent in the left ulnar artery. On numerous examinations the serologic test for syphilis was negative and the blood pressure was always normal. Since the age of 28 he had had episodes of mania, depression, obsessions, and disorders of affection. In 1929 neurologic examination was negative; there was, however, some evidence of an affective disorder at that time. According to a letter from his physician in January 1934, he had had transitory aphasia and disorientation, and in 1935 he had experienced numbness of the left upper and lower extremities. In October 1935, neurologic examination showed diminished sensations

in, and diminished power and atrophy of the muscles of, the lower extremities. This was considered to be due to neuritis. The patient was reëxamined at the clinic on several occasions, the last one being in October, 1936, at which time amputation of the right leg was necessary.

Case 11. A man, 52 years old, had had intermittent claudication involving the lower extremities beginning 20 years earlier. Amputation of both legs below the knees had been performed. For five years he had attacks of pain in the abdomen for which three exploratory operations had been performed. No organic disease was found. Since the age of 48 he had noticed color changes of a vasospastic nature in the fingers of both hands, and trophic lesions finally affected his fingers. At the time of examination at the clinic the patient complained chiefly of pain in both hands. Examination revealed absence of pulsations in the radial and ulnar arteries and in the popliteal arteries bilaterally. Pulsations were diminished in the left femoral artery. The blood pressure was 110 systolic, 85 diastolic. There was no evidence of diabetes or syphilis. Ulcerations were present on some of the fingers. Hemianopia was also present. A diagnosis of thrombo-angiitis obliterans was made and, after treatment with repeated intravenous injections of typhoid vaccine to induce fever artificially, and after other measures, cervicothoracic sympathectomy was performed. Convalescence was satisfactory until the twenty-second day following operation when the patient noted the sudden onset of numbness on the left side of his body associated with a marked reduction in motor power. These symptoms persisted for three days and disappeared spontaneously. The hemianopia disappeared after operation. The patient left the clinic much improved but, one year later, wrote that he was having episodes of pain suggestive of angina pectoris and further trouble with vascular disease involving his upper extremities.

It is admitted freely that some of our patients were in the age group in which sclerotic changes might be present. The patients in cases 1, 10 and 11 were 50 or more years old, although in the first case the inflammatory nature of the lesions in the extremities was proved microscopically and in the tenth case the disease was first manifest when the patient was 45 and superficial phlebitis had occurred. In all of our cases there was distinct evidence of organic intracranial disease. In case 10 episodes of aphasia, disorientation, and numbness of the left upper and lower extremities were highly suggestive of organic intracranial disease.

The diagnosis of thrombo-angiitis seemed warranted in all cases, although the possibility of the diminished circulation to the extremities being due to arteriosclerosis in some instances, cannot be denied. Hypertension was present in cases 5, 7 and 9 and may possibly have been responsible for the cerebral lesions, although we do not believe so. In all other cases hypertension was absent. None of the patients had diabetes. In case 6 there was a history of syphilis; a flocculation test on the blood was positive while that on the spinal fluid was negative. In all other cases flocculation tests on the blood were negative. Since there was no evidence of syphilis of the central nervous system in case 6, we do not believe the cerebral vascular lesions were due to syphilis.

The duration of the peripheral disease in our group of cases varied from five months to 20 years. In most of the cases the cerebral complications occurred following the onset of the peripheral disease. The cerebral lesion

preceded the peripheral symptoms in only three cases (5, 7, 8). In these three cases the hemiplegia was present two, one, and fourteen years, respectively, before the onset of the peripheral symptoms. Thrombo-angiitis obliterans must therefore be suspected in cases of cerebral vascular disease of obscure etiology.

The outstanding symptom from the neurologic standpoint was hemiplegia which occurred transiently, one or several times, or permanently. In some cases there were such symptoms as confusion, disorientation, aphasia, and loss of memory, symptoms which frequently cleared up entirely. Hemianopia, which was present in cases 1 and 11, disappeared following sympathectomy in one case (case 11). This is similar to the case reported by Foerster and Guttmann.

The symptoms of thrombo-angiitis in the brain depend chiefly on where the lesion is located in the brain, and this may vary from case to case. Certain manifestations of the disease, however, are predominant and fairly characteristic of cerebral involvement. In many cases some of the manifestations of cerebral involvement are transient and disappear entirely. Psychic changes, such as confusion and loss of memory, may be associated with signs of organic involvement of the brain. Hemiplegia may occur repeatedly or persist. The transient nature of the symptoms may be due to arterial spasm superimposed on a thrombotic lesion or to rapid development of collateral circulation after thrombosis. Very interesting was the prompt effect of operation on hemianopia in Foerster and Guttmann's case and in our case 11.

Our 11 patients with cerebral involvement were from a group of 500 with thrombo-angiitis obliterans of the extremities. While this percentage of cerebral involvement is only about 2.0, it may be found that this complication occurs more frequently if attention be directed to it. This study emphasizes that cerebrovascular complications may occur in cases of thrombo-angiitis obliterans and may precede evidence of the thrombo-angiitis obliterans of the extremities. It is also apparent that peripheral thrombo-angiitis obliterans may be the least serious part of a disease which may be disabling or may terminate life as a result of involvement of such vital structures as the brain and heart.

Summary

To reports of 23 cases of thrombo-angiitis obliterans with involvement of the brain which have been collected from the literature, reports of 11 cases observed at The Mayo Clinic have been added. Too little evidence relative to the nature of the pathologic process in the brain is available, but it may be sclerotic alone, both inflammatory and sclerotic, or inflammatory alone. Hemiplegia, hemianopia and psychic changes are common manifestations of cerebral involvement in thrombo-angiitis obliterans, and the disappearance and recurrence of these symptoms is occasionally striking.

It is apparent that thrombo-angiitis obliterans may be a widespread disease and that involvement of the peripheral vessels may be, for some individuals, the least important part of a disease which may involve such vital structures as the heart or brain.

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CARDIOVASCULAR CHANGES ASSOCIATED WITH THE INSULIN SHOCK TREATMENT*

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ALTHOUGH Sakel's insulin "shock" treatment for schizophrenia has been receiving increasing recognition during the past three years, and has already been employed in thousands of cases, there have appeared comparatively few thorough or exhaustive works regarding the physiological changes associated with this method of therapy. This has been especially true as regards the description of changes in the circulatory system. No doubt this has been to a large extent due to the preoccupation of the various workers with the psychic rather than physical changes undergone by the patients, during and after the course of insulin "shock." Also Sakel has specifically admonished his followers against unduly disturbing the patients with unessential tests or examinations during the treatment, inasmuch as this would interfere with their obtaining and maintaining an optimal state of "shock." This prohibition must have led to the failure of many workers to recognize certain definite circulatory changes which a closer degree of observation would undoubtedly have disclosed. Consequently, it is not surprising that the most thorough and reliable studies on circulatory changes under the influence of insulin have been conducted by workers such as Weichmann and Koch,[1] Brandt and Katz,[2] Romano, Mazzei and Baila,[3] who approached the subject from the experimental angle, rather than under the clinical conditions of the Sakel regimen.

It is our purpose in this paper to collect and organize the data available at present regarding the changes in the circulatory system during prolonged insulin hypoglycemic treatment and to amplify and confirm some of these findings with the material obtained from our own observations. Our own observations were based on the detailed study of a group of male patients, all suffering from schizophrenia or allied types of mental disorder, ranging in age from 25 to 52 years, the average age of the group being 40 years. There were 49 patients in our group, and of these 30 were at one time or another under the personal observation of the writer, while the others were being specifically observed by other physicians who were temporarily assigned to the hypoglycemic ward for six-week periods. The patients under discussion have undergone hypoglycemic treatments for periods ranging from 20 to 85 days. Since with but two exceptions (B. V. D. and G. W.) our patients were world war veterans, they were as a group considerably older than those being treated in other neuropsychiatric institutions (such as

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state and city psychopathic hospitals). Also their psychoses were of much longer duration than is the rule in younger groups of patients, usually having been manifest for between 15 and 20 years. However, we have no reason to believe that the physiological changes we shall discuss are not equally valid for younger groups of patients, especially since on our visits to other institutions where younger patients, both male and female, were being treated, we have frequently observed similar physical findings. All our patients had been thoroughly examined before the institution of insulin treatment from the physical, roentgenologic and electrocardiographic angles and presented no prior evidence of definite disease or abnormality of the cardiovascular system.

In order to achieve a systematic presentation of our subject we shall consider our data under the usual headings of physical findings, roentgen-ray, and electrocardiographic changes.

It is particularly worthy of note that the changes which we consider characteristic of the insulin effect may appear as early as one hour and 17 minutes after the first intramuscular injection of 10 units of insulin (see table 1, G. W., case 39).

Part I: Physical Findings

A. Review of Literature. Apparently the first careful study of the circulation in humans during the hypoglycemic state (arising spontaneously or experimentally produced), was made by Weichmann and Koch [1] in 1928. Their conclusions merit quoting at some length:

"(1) In the hypoglycemic attack after insulin injection the venous blood on withdrawal from the unobstructed (i.e. by a tourniquet) cubital vein is strikingly light red. Often the arterial and venous blood are indistinguishable. One gains the impression not only that 'arterial' blood flows out of the vein, but also that it flows out under an increased pressure, that is, it spurts out. The bleeding from the point of puncture of the vein is more difficult to stop than is usually the case. One feels that one can see the arterial pulse pounding through to the venous side. The medium erythrocyte diameter of the venous blood approaches closely that of the arterial blood. This finding is explained through a relaxation of the vascular tone. The vascular channels open themselves to an extraordinary extent and as a consequence the blood flows more rapidly. An increase of the minute volume is to be assumed from this.

"(2) In 13 cases which were examined in the hypoglycemic state an acceleration of the pulse could be noted; in two cases the pulse frequency was unchanged; in three cases it was slow. A parallelism between the eventual pulse quickening and the status of the blood sugar level was lacking throughout. Often the pulse frequency reached the maximum of its acceleration only after the taking on of nourishment, when the blood sugar value had already returned to normal. The cause of the pulse frequency can therefore not be attributed to the hypoglycemia as such.

TABLE I

Initials Case No.	Blood Pressure Before Insulin Treatment	Day of Treatment	Observations Made During Insulin Treatment					Observations Made After Insulin Treatment		
			Dose of Insulin	Given at	Clinical Findings	Blood Pressure	Time of Reading	Number of Days Since Last Treatment	Clinical Findings	Blood Pressure
C. W. 10	132/90	69th	180 units	7:06 a.m.	No definite murmurs	110/76	7:34 a.m.	40 days	No murmurs	126/76
					Moderate to and fro aortic murmurs, pistol shot at brachial.	144/0	9:30 a.m.			
W. C. 2	128/80	55th	140 units	7:20 a.m.	Marked to and fro aortic murmur	128/56	8:02 a.m.	14 days	No murmurs	132/74
					Marked to and fro aortic murmur, loud pistol shot at brachial.	150/58	9:16 a.m.	40 days	No murmurs	146/78
		56th	160 units	7:15 a.m.	Moderate to and fro aortic murmur	118/56	7:50 a.m.	65 days	No murmurs	138/75
					Corrigan pulse; marked to and fro aortic murmur; capillary pulsation; pistol shot at brachial	162/0	9:20 a.m.			
H. B. 22	125/90	26th	40 units	7:22 a.m.	No murmurs	96/60	7:05 a.m. (before insulin injection)	7 days	Moderate to and fro aortic murmur; slight capillary pulsation; bounding pulse	122/54
		28th	80 units	7:18 a.m.	Moderate to and fro aortic murmurs	116/56	10:30 a.m.	34 days	No murmurs	118/72
		35th	170 units	7:08 a.m.	Moderate to and fro aortic murmurs	106/56	7:32 a.m.	59 days	No murmurs	110/66

TABLE I (*Continued*)

Initials Case No.	Blood Pressure Before Insulin Treatment	Day of Treatment	Observations Made During Insulin Treatment					Observations Made After Insulin Treatment		
			Dose of Insulin	Given at	Clinical Findings	Blood Pressure	Time of Reading	Number of Days Since Last Treatment	Clinical Findings	Blood Pressure
B. V. D. 4	125/80	66th	140 units	7:23 a.m.	No murmurs	118/82	8:13 a.m.	7 days	Marked to and fro aortic murmur; bounding pulse; slight capillary pulsation	144/84
		74th	160 units	6:35 a.m.	Definite to and fro aortic murmur	130/56	10:10 a.m.	59 days	Soft systolic murmur at pulmonic area	134/70
T. M. 21	114/70	36th	330 units	7:21 a.m.	No murmurs	115/70	8:07 a.m.		Treatment still going on	
		54th	170 units	6:36 a.m.	Moderate to and fro aortic murmurs	134/54	8:46 a.m.			
		65th	130 units	6:45 a.m.	Moderate to and fro aortic murmur	122/72	2 p.m.			
G. W. 39	115/70	1st	10 units	6:41 a.m.	Soft to and fro aortic murmur	106/0	7:57 a.m.		Treatment still going on	
					No murmurs	102/68	8 a.m.			
		12th	100 units	6:40 a.m.	Moderate to and fro aortic murmur	126/55	8:46 a.m.			
		23rd	90 units	6:46 a.m.	Soft aortic diastolic murmur	112/78	2 p.m.			
B. H. 7	94/60	53rd	110 units	7:19 a.m.	Marked to and fro aortic murmur	116/0	7 a.m.	61 days	Moderate to and fro aortic murmur	108/80
					No definite murmur	116/70	2:45 p.m.	105 days	Moderate to and fro aortic murmur	146/92

" (3) In the great majority of cases the systolic as well as the diastolic pressure sinks in the hypoglycemic state. In a number of cases, the diastolic pressure sank even more than the systolic. The pulse pressure increased. Since all these changes were not only limited by the hypoglycemic state, but also often remained after the ingestion of food, it is justifiable to assume that they are not merely the result of the lowered blood sugar level, but also of the insulin action per se. Among conditions which can play a rôle in the development of this hypotension associated with hypoglycemia are discussed: disturbances in myocardial function, diminution of the total blood volume, diminution of the blood viscosity, and abnormal changes in diameter of the small and smallest blood vessels.

" (4) In the hypoglycemic attack there can be heard transitory aortic diastolic murmurs. In four cases during the hypoglycemic attack, a definite diastolic murmur was audible over the aortic area, which later again disappeared, and was not to be heard in the fasting state. The pulse was *celer*. The blood pressures in these cases were respectively, fasting—125/68, 145/80, 118/69, and 236/111. In the hypoglycemic attack we found them 125/35, 115/40, 122/36, and 207/73. On percussion, the heart seemed to be enlarged to the left."

In their work published in 1929, Lauter and Baumann [4] in the main confirm the observations of Weichmann and Koch. They again point out that the minute volume is increased in the hypoglycemic state. They add the significant finding that this increase begins even before the obvious clinical symptoms of hypoglycemia appear, and only subsides several hours after the administration of carbohydrate. They further point out that although the venous blood in many cases is strikingly bright red, and shows a smaller oxygen deficit than in the normal, still the oxygen utilization is not at all diminished but either normal or increased. This they explain on the basis of the increased velocity of the blood flow.

Later writers do not seem to have added much that is significant to the above descriptions. Of course, Sakel [5] and his co-workers have noted the appearance of tachycardia, bradycardia, indeterminate arrhythmias and increased pulse pressures, and have delimited rather arbitrarily the " safe " limits for their fluctuation during the insulin treatment for schizophrenia. On the other hand, we find the following statement in Hadorn's paper [6] published in September, 1936, based on the examination of 31 patients undergoing the shock treatment: " The percussion and auscultatory findings showed no change after insulin, except for frequency and rhythm changes."

B. Clinical Observations Under Insulin Shock Treatment. In comparing the following observations with those made by Weichmann and Koch, etc., the differences between therapeutic insulin hypoglycemia, and the experimental hypoglycemias produced and observed by the earlier authors must be borne in mind. In the first place experimental hypoglycemias were rarely maintained more than an hour or two at the most, while therapeutic

hypoglycemia is routinely maintained for four or five hours or longer; in the second place, experimental hypoglycemias were rarely repeated more than a couple of times in the same individual subjects, while therapeutic hypoglycemia has been induced repeatedly for weeks and months in individual schizophrenic patients. In fact one of our patients had been treated with relatively large doses of insulin for 85 treatment days. Consequently, it is but to be expected that more frequent, more constant, more profound, and perhaps more lasting cardiovascular changes will be found in the latter instances.

From our own experience and observations we have derived the following picture of the patients' state under therapeutic hypoglycemia. We find it convenient to divide the vascular physical findings into two groups: those attributable directly to variations in the vasomotor tonus, and those attributable directly to changes in the cardio-aortic region itself. Within a few minutes after the intramuscular injection of insulin in effective doses there begin to appear vascular evidences of altered activity of the vegetative nervous system, in the sense of varying degrees of balance between the sympathetic and parasympathetic activity. On inspection, the *color* of patients shows marked variations. Some show a facial flush of fluctuating intensity throughout the course of (as well as after) the hypoglycemia. Others show predominantly a pallor during the course of the hypoglycemia. Others show comparatively little alterations from their usual appearance. The majority of cases show an intermediate degree of intensity of flushing and fluctuations between flush and pallor. The flushing usually shows marked regional variations, usually being most pronounced in the head and neck, and in most cases also involving the hands and feet. In the *typical* case the flush predominates in the pre-comatose (drowsy, somnolent) stage, and in the stage of light coma (muscular tonicity, extensor spasms, involuntary stereotyped movements, excitement), while pallor predominates in the stage of deep coma (muscular relaxation, absent corneals, positive Babinskis). After termination normal or ruddy facies are again the rule. Of course, cyanosis develops whenever there is interference with respiration due to convulsive or prolonged tonic reactions, accumulation of mucus in the air passages, etc. Since many patients show spontaneous fluctuations in the depth of their coma, they usually show corresponding changes in color. Often, we have observed the development of a circumoral, nasal, and circumnasal pallor, which gives the patient a "drawn" appearance suggesting the hippocratic facies. In one case (C.C.), we have observed repeatedly a "butterfly" flush involving symmetrically both cheeks and the middle region of the forehead, while the nose itself and circumoral region and remainder of the face had the usual pallor.

As regards changes occurring in the cardio-aortic region itself we have found symptoms and signs presenting themselves, which undoubtedly are the effects of a *varying* and *variable* degree of dilatation in the region of the aortic bulb and ascending aorta. On inspection we quite regularly see an

increased degree of peripheral vascular pulsation. An increased venous pulsation in the neck is also usually evident. Along with this we find that the pulse assumes a " bounding " character, and associated with this we find an increasing pulse pressure chiefly dependent upon a drop in the diastolic blood pressure. As the diastolic pressure drops further and often ultimately reaches zero the pulse assumes a definite " Corrigan " character. When this occurs we usually can hear a " pistol shot " sound over the brachial artery and at times a " Duroziez " murmur over the femoral artery. Occasionally even a capillary pulsation becomes apparent. On a few occasions when the above phenomena were most pronounced, we have felt a systolic thrill over the brachial artery. With careful auscultation we can usually make out a to and fro murmur which seems to originate over the aortic region and is transmitted down the left border of the sternum and out towards the apex. The systolic component of the murmur is usually most evident, while the diastolic component varies from the faintest whiff accompanying the second sound, to a fairly well defined aortic regurgitant murmur. In some cases (particularly when the *systolic* pressure remains unusually low), we can only make out a single sound at the base, suggesting that there is insufficient impact against the semilunar valves or such a degree of insufficiency, as to produce no audible second sound. From such findings we may surmise that there is also associated with the aortic dilatation, a similar dilatation of the pulmonic conus. These findings, we must repeat, are found to be present to a variable degree in different patients, and in the same patient. However, they may appear very soon after the injection of insulin, and even after the first dose. Thus, with patient 39, G. W., a blood pressure of 106/0 was obtained one hour and 16 minutes after the first injection of ten units of insulin, while three minutes later the reading was 102/68. In perhaps 30 per cent of our patients the aortic dilatation phenomena were readily detectable on almost any occasion, after the treatment was well established. In the others the more evanescent character of the phenomena was demonstrated by the fact that they were found only occasionally, and only because these patients were examined day after day during various phases of the treatment. Thus, in personally following a series of 16 cases under intensive treatment for a period of six weeks, the writer was able to detect the findings of aortic dilatation at one time or another, in all but one case. In most of these cases, these phenomena persisted for various periods of time after the termination of the hypoglycemia, but invariably the findings were less marked the longer the time interval between the last hypoglycemic period and the date of observation. As a rule, the abnormal pulse pressures showed the recession to the normal levels first, while the murmurs persisted for a considerably longer period. In the accompanying table 1, we have indicated certain of the more typical clinical findings in individual cases. Sufficient data are given there to show that the findings in any specific case at any particular time are entirely unpredictable. The phenomena of aortic dilatation may be either evident or absent, whether in the morning before the insulin

injection has been given, or in the afternoon several hours after termination, or during the various phases of hypoglycemic shock; and finally these phenomena in some cases may persist for several months after the use of insulin has been discontinued (see figures on case 7, B. H.). However, as a rule the aortic dilatation phenomena show a progressive diminution in intensity as time goes on.

The question of pulse frequency and rhythm during the hypoglycemic shock treatment has been thoroughly covered by previous writers. Our observations are essentially in agreement with these previous reports. We have found usually a slight progressive acceleration of the pulse rate during the somnolent and excitement stages (stage of light shock), with a tendency to relative slowing during the stage of deep shock, and again a tendency towards moderate acceleration for a couple of hours after termination. Only very rarely have we observed tachycardias above 130 or bradycardias below 50. The rhythm is usually grossly regular, the only abnormality fairly frequently observed being a sinus arrhythmia. Occasionally, infrequent extrasystoles have appeared,—but we have not observed any more serious disturbances in rhythm in any of our patients.

In seeking for a physiological explanation of the cardiovascular changes, particularly the aortic dilatation phenomena during the hypoglycemic treatment, we have found the following material which illuminates this question. It has long been known that insulin hypoglycemia calls forth a physiological outpouring of adrenalin into the blood stream. Brandt and Katz [2] in 1933, proved directly the existence of this compensatory adrenalinemia by biological and chemical tests. In one of their typical case protocols they show that the maximum adrenalin effect appeared 34 minutes after the intravenous injection of 30 units of crystalline insulin. Meythaler [7] in 1935, showed that compensatory adrenalinemia appears after the intravenous injection of small doses (a few units) of insulin, long before the blood sugar level has reached the critical so-called hypoglycemic range. That is, that with every *decline* of the blood sugar level in the blood, regardless of the original level, the adrenalin output is increased. This finding, of course, explains why the symptoms of adrenalin activity appear so soon after the insulin injection, even while the blood sugar level is still fairly normal. An explanation of the actual aortic dilatation phenomena is then found in the work of J. Gottesman and J. Pal [8] as described in the latter's paper in 1935. These workers showed that within three to eight minutes after the subcutaneous injection of 0.001 gm. adrenalin there appeared pulsus *celer* and *altus*, a diastolic pressure of zero, and the typical murmurs, all of which they state are due to an active widening of the ascending aorta. This change, Pal asserts, is a regular manifestation of the stimulation of the sympathetic innervation of the cardio-aortic region. The bradycardia usually seen during the phase of "deep" shock is also attributable to adrenalinemia, as the cardio-inhibitory function of adrenalin (operating via the vagus), is well established.[9]

Reasoning conversely from the above facts, the inference may be made that as long as aortic dilatation phenomena persist in any individual case, an adrenalinemia very likely remains associated with them. It is particularly important to establish this point since our clinical studies have shown that the aortic dilatation phenomena may persist for weeks and even months after the completion of the hypoglycemic treatment. It is our purpose in subsequent studies to determine directly the extent of persistence of adrenalinemia.

Since insulin has been known to precipitate coronary attacks in cardiac patients [10, 11] and moreover since S. A. Levine has proposed the use of the "adrenalin test" for distinguishing between true and pseudo-angina pectoris, does not this view of the cardio-aortic changes during the hypoglycemic treatment indicate that we are exposing our patients to an excessive danger of cardiac accidents? To this question we can answer by stating that experience has shown that no such danger is present in properly selected cases. Our own experience particularly bears this out, since we have dealt with a group of patients whose average age is 40 years, and still have had no untoward cardiac complications. As long as Dr. Sakel's list of contra-indications for his treatment are borne in mind, we feel one should have no undue apprehension on this account.

Part II: Roentgen-Ray Findings

A survey of the literature available at this time indicates that hitherto no attempts have been made to follow the cardiac changes during the hypoglycemic treatment, with the roentgen-ray. This is not surprising when one considers the practical difficulties which one encounters in attempting to secure roentgenograms of the heart at different times under sufficiently fixed conditions so that the measurements may be compared with a reasonable degree of accuracy. In order to achieve this purpose, it is above all necessary to have fairly coöperative patients who will at least make an attempt to hold their breath at deep inspiration during the period of exposure. Such suitable coöperation is especially difficult to obtain with psychotic patients. To eliminate as far as possible the error due to this factor, we selected for this study 10 patients, who, we felt, would coöperate best during the taking of the roentgen-ray picture. On these patients a total of 26 standard six-foot flat heart plates were taken. Films were taken before, during, and after the course of hypoglycemic treatment. Unfortunately, no films could be taken during the actual hypoglycemic state, since it was impracticable to transport patients during hypoglycemic shock, and since our portable roentgen-ray apparatus could not be adapted to take sufficiently accurate six foot heart plates. Consequently, it must be borne in mind, that those plates listed as being taken "during the course" of the hypoglycemic treatment were actually taken while the patients were on an ambulatory status, i.e., in the afternoon after termination or on a rest day. As a check on the standardization of conditions under which films to be com-

pared were taken, we decided on the following criteria: first, the transthoracic diameter in each film was to vary not more than five millimeters from the film with which it was to be compared; second, the level of the diaphragm in films which were to be compared had to be essentially similar. Because of the strict adherence to these criteria, we found it necessary to eliminate 12 of the 26 films from our study. However, because of these precautions the margin of technical error involved in our method is reduced to a theoretical 2 per cent. Consequently, any difference in measurements greater than 2 per cent may be considered significant as regards actual physical change. The results of our studies on the 14 films (taken on six different patients), which were suitable for comparison, are listed in table 2. Wherever possible (as in cases 2, 7, and 22), the total transverse measurement of the aortic arch was used as an indicator of the changes occurring at the base of the heart. In the three other cases this measurement could not be used because the right border of the aortic arch could not be clearly defined, inasmuch as it was transposed over the dense shadow of the vertebral bodies. Consequently, in these cases we used the "Upper Left Margin" measurement as defined in the table.

Table 2 shows that in all cases in which comparable films were available, a significant increase in the diameters of the heart appears during the insulin treatment, and evidently may persist for at least two months after the conclusion of the prolonged course of treatment. The increase is evidently more marked in the basal region of the heart than in the apical region of the heart (the figures ranging from + 4 per cent to + 24 per cent in the former case, as compared to figures of 0 to + 14 per cent in the latter case).

Although the measurements given above indicate a distinct increase in the cardiac diameters, in no case do they reach values that are ordinarily considered pathological (viz. aortic arch measurements exceeding 8 centimeters, or a cardio-thoracic ratio exceeding ½). All in all the roentgen-ray changes thus far found coincide fairly well with the physical changes described in Part I of this paper.

Part III: Electrocardiographic Findings

Perhaps more has been done in the way of electrocardiographic studies during hypoglycemia, than in any other phase of this problem. Before the introduction of the Sakel treatment, numerous reports appeared describing the changes occurring in hypoglycemic attacks in diabetics as well as in experimental hypoglycemias. An excellent summary of this early work is found in the paper of Romano, Mazzei and Baila,[3] who in addition report their own careful observations on 30 normal subjects given 15 units of insulin intravenously. The earlier reports agree substantially in reporting most frequently "T"-wave changes in the way of flattening or inversion. In addition, mention is made in the individual reports of P-wave changes, widening of the QRS complex, and occasionally disturbances in rhythm

Roentgen-Ray Studies

TABLE II

Roentgen-Ray Studies

Initials / Case Number	Total Number of Treatments / Date Treatment Ended	Roentgen-ray Findings Before Treatment	Date	Roentgen-ray Findings During Treatment	Date	% Change	Roentgen-ray Findings After Treatment	Date	% Change	Remarks
B. V. D. 4	85 8-13-37	U.L.M. = 4.8 cm. C.T. = 12.5 cm. / 33.2 cm.	2-16-37	None available			U.L.M. = 5.6 cm. C.T. = 14.3 cm. / 32.8 cm.	9-27-37	+17% +14%	
							U.L.M. = 5. cm. C.T. = 13.6 cm. / 33.3 cm.	10-11-37	+4% +9%	
W. C. 2	75 8-6-37	A.A. = 6.5 cm. C.T. = 12.4 cm. / 30.6 cm.	1-14-37	A.A. = 7. cm. C.T. = 13.3 cm. / 30.6 cm.	7-12-37	+8% +7%	None available			
B. H. 7	54 6-26-37	A.A. = 5.7 cm. C.T. = 12.1 cm. / 30. cm.	2-25-37	None available			A.A. = 6. cm. C.T. = 12.2 cm. / 29.8 cm.	9-2-37	+5% no significant change	
H. B. 22	50 8-13-37	A.A. = 4.7 cm. C.T. = 11.5 cm. / 30.6 cm.	3-23-37	None available			A.A. = 5.1 cm. C.T. = 12. cm. / 30.7 cm.	9-1-37	+8% +4%	Between the dates of these two roentgen-rays, the patient was placed on ground parole and was permitted considerably more physical activity. This may be a factor in the progressive increase in cardiac measurements after treatment was terminated.
							A.A. = 5.4 cm. C.T. = 12.2 cm. / 30.7 cm.	10-12-37	+15% + 6%	
T. M. 21	being continued	U.L.M. = 5. cm. C.T. = 12. cm. / 30.2 cm.	1-13-37	U.L.M. = 6.2 cm. C.T. = 12.3 cm. / 30.3 cm.	9-2-37	+24% +2½%	Treatment being continued			
P. N. 25	62 8-12-37	U.L.M. = 4.7 cm. C.T. = 10.9 cm. / 27.8 cm.	3-4-37	None available			U.L.M. = 5.2 cm. C.T. = 12. cm. / 28. cm.	10-12-37	+11% +10%	

Glossary: U.L.M. = Upper left margin measurement (always taken at lower border of third intercostal space).
A.A. = Aortic arch measurement (total)—(always taken at lower border of second intercostal space)
C.T. = Cardio-Thoracic Ratio measurements, consisting of the $\frac{\text{Transverse Diam. of the Heart}}{\text{Transverse Chest Diameter}}$.

such as bradycardia, alternation, auricular and ventricular extrasystoles, sinus arrhythmia, and exceptionally, disturbances in conduction. Some writers also mention changes in voltage (usually increase), of the R- and S-waves.

Romano and his co-workers reporting on their own material of 30 cases noted:

(1) Increased frequency in 83 per cent of their cases.

(2) Increased voltage of the P-wave in three cases, diminution in one case, inversion in one case.

(3) Increased voltage of R_2 and R_3 six times, increase of S_2 in two cases and diminution of S_3 in two cases.

(4) Appearance of a small " U "-wave on two occasions.

(5) Diminution of the height of the " T "-wave in 27 of the 30 cases. (This includes negativity in many instances.)

They particularly point out that in spite of the fact that these alterations were in many cases quite definite, they did not produce any angina pectoris or phenomena of cardiac decompensation in any of their healthy subjects.

DeChatel and Palisa,[12] working in Sakel's clinic, on 19 schizophrenic patients undergoing the hypoglycemic treatment, noted invariably that " T "-wave changes occurred consisting of lowering of the " T "-wave, and in all cases definite inversion in Lead IV. In two cases they observed a very marked sinus arrhythmia, but no other disturbances of conduction. They found that the electrocardiographic changes were most evident after 45 minutes from the time of injection of the insulin, and persisted until perhaps one-half to one hour after the termination of the coma.

W. Hadorn [6] of Bern, Switzerland, studied 31 patients undergoing the hypoglycemic shock treatment and found significant electrocardiographic changes in almost two-thirds of these cases. These consisted of arrhythmias of minor significance, lowering of ST, flattening and sometimes negativity of the T-wave, widening of the QRS, and occasional appearance of U-waves. He too finds that these changes are usually reversible.

Our own limited experience agrees quite closely with the findings of these previous workers. We took 12 electrocardiograms during the course of treatment which could be compared with graphs taken just before the beginning of treatment. We noted no P-wave changes; an increase of Q_3 in two instances; an increase in R voltage in four instances; a diminution in R voltage in two instances; lowering of the T-wave in two instances; negativity of T_2 and T_3 in two instances; increased voltage of T-wave in one instance (graph taken on a rest day); marked sinus arrhythmia in two instances; infrequent left ventricular extrasystoles in one instance; slight widening of the QRS in two instances (from 0.06 sec. to 0.08 sec. and from 0.08 sec. to 0.10 sec. respectively). None of the more significant changes, viz., the T-wave negativity and pathological Q_3, were found in any case except during the phase of shock.

It is generally agreed that the electrocardiographic changes noted above are evidences of states of myocardial mal-nutrition or anoxemia. Obviously, insulin hypoglycemia operates to produce this effect at least in part by removing in large measure the carbohydrate which the heart muscle needs. However, Hadorn [6] has shown that this is not the only factor, since he was able to produce similar changes in the " T "-waves when he injected glucose intravenously along with the insulin. Also, the persistence of the EKG changes for some hours after the termination of the hypoglycemic state is evidence for the existence of some other cause. This cause is, most likely, again the adrenalin effect, which operates to produce a myocardial ischemia by bringing about the reduction in diastolic pressure which prevents proper filling of the coronary arteries.

Summary

During the course of insulin hypoglycemic treatment profound changes arise in the cardio-vascular system, which have been inadequately described in previous reports regarding this method of therapy.

A review of the literature regarding experimental and spontaneous hypoglycemia shows that most of these changes have been observed from time to time in rare instances. The work of Weichmann and Koch is cited as giving the most comprehensive account of the cardiovascular changes in experimental hypoglycemia. These changes consist of: peripheral vasomotor phenomena, which are best explained by variations in the activity of the several parts and regions of the vegetative nervous system; and cardio-aortic phenomena which are best explained as a result of the adrenalinemia produced by the action of insulin. The cardio-aortic changes consist primarily of an active widening of the aortic bulb and ascending aorta which may develop to such a degree as to produce typical symptoms and signs of aortic insufficiency. These changes were all found to be reversible, though they persist for varying periods of time after the termination of experimental hypoglycemia.

Our own work on 49 patients undergoing the Sakel regimen for schizophrenia, proves that essentially similar physiological changes, viz. the vasomotor phenomena and the cardio-aortic dilatation phenomena, appear quite regularly at one time or another during the course of this treatment. The persistence of these changes, albeit in a progressively diminishing degree, for weeks and months in certain cases, is also demonstrated. The trend in all cases seems to be towards a reversibility of these cardiovascular changes, so that they may be considered physiological rather than pathological in significance.

Roentgen-ray studies taken during and after the course of the hypoglycemic treatment afford concrete confirmatory evidence of the occurrence of these cardio-aortic changes. These studies demonstrate a relatively greater increase in the basal as compared with the apical diameters of the heart, and in the main, coincide with the clinical physical findings.

Our electrocardiographic studies are in accord with those described by previous authors, notably W. Hadorn [6] and Romano, Mazzei and Baila.[3] The most frequent electrocardiographic abnormalities in hypoglycemia are seen to be flattening and inversion of T-waves, and sinus arrhythmias. Other changes which have been noted are pathological " Q_3 "-waves, changes in R and S voltage, slight widening of the QRS complexes, appearance of " U "-waves, appearance of auricular and ventricular extrasystoles. The theoretical implications of these changes are discussed in the text.

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POSSIBILITIES IN BIOLOGICAL ENGINEERING*

By KARL T. COMPTON, *Cambridge, Massachusetts*

WHEN I asked myself why I, a physicist, should be invited to address you, America's most distinguished body of physicians, I found an answer extending back over many centuries. For physics and medicine have been closely associated from their very beginnings. The words physics and physician both derive from the Greek root meaning "that which pertains to nature" as distinguished from the spiritual, mental and moral world. Webster's Dictionary gives two definitions of "physicist": first, one versed in medical science; second, one versed in natural science. In France I, as a physicist, would be called a physicien. In Germany I would be a physiker which, in English, is one who administers a physic.

In the early days of science there was little differentiation between the study of animate and inanimate phenomena; the great scientists of the day concerned themselves indiscriminately with medicine, physics and alchemy. But, as knowledge of natural science grew, specialization became necessary in the three great fields of biology, physics and chemistry. Medicine and engineering emerged as combinations of art and applied science, medicine being based largely on biology and engineering on physics.

It has been the history of science that this tendency to specialization and differentiation into different fields is frequently followed by a merging together again. This happens when some fundamental discoveries disclose the underlying unity of two branches of science which had hitherto developed on less fundamental and apparently unrelated bases. The best example of this is in physics and chemistry. A generation ago it was easy to distinguish a physicist from a chemist. One dealt with matter in bulk and the other with changes in molecular constitution. There still exists a difference between what might be called the plumbing type of physics and the culinary type of chemistry, but in their interpretive and many of their operational aspects the two sciences are now completely merged, to their very great advantage.

I think we all believe that there is a basic unity of interpretation and understanding underlying all phenomena of the material world. It is only our ignorance or lack of skill which forces us to proceed along different lines, based on different sets of fundamental laws. With increasing knowledge these barriers break down, and new lines of attack are opened up with new weapons. My purpose, in this address, is to discuss the possibilities of a closer working liaison between the biological, physical and chemical sciences, together with their applied aspects in medicine and engineering.

* Convocation Address, Twenty-Second Annual Session, American College of Physicians, New York, April 6, 1938, by Karl T. Compton, President, Massachusetts Institute of Technology.

The opportunities for such liaison may be illustrated by two examples. Consider the technic of the physician in a clinical examination. He takes the patient's temperature and pulse rate, listens with a stethoscope to his heart and lung action, examines his eyes, nose and throat with optical instruments, takes an electrocardiogram and a series of roentgen-ray photographs. Thus far he uses instruments devised by physicists. He also employs chemical methods in analyses of blood, urine, metabolism and perhaps tests the spinal fluid. If he prescribes a treatment other than diet, rest, exercise or abstinence from tobacco, it is likely to be physical therapy with roentgen-rays, heat or ultraviolet light, or chemical treatment with medicines.

Bone disorders are detected and observed by roentgen-rays. The processes of bone metabolism are affected by diet, by glandular action stimulated by chemical hormones like parathormone and by ultraviolet light. The exact operation of these processes may be studied by use of chemical isotopes or radioactive chemicals produced and detected by physical methods and used as tracers. If we wish, for example, to study in detail the body process between the drinking of water and its effect, if any, on the joints, we could give the patient a little "heavy water," containing deuterium instead of hydrogen, and trace this deuterium as it proceeds in metabolism to the various fluids and tissues of the body. Or, similarly, we can produce artificial radioactive calcium or phosphorus by the modern alchemy possible with proper use of very high voltage equipment; feed this calcium or phosphorus in food to the patient or experimental animal, finally detect quantitatively and with marvelous sensitiveness the rate at which this material deposits in the bones, with aid of physical instruments which were originally devised for experiments on cosmic rays and for measuring the geological age of rocks.

These two illustrations, chosen from the field of medicine, could be matched by many others from the allied life sciences comprised under the general head of biology. For example, the physical agent roentgen-rays and the chemical agent calcodine have opened up entirely new vistas in genetics. Bacteriology and mechanical engineering are revolutionizing the food processing industries. We now have yeast and mould cells being bombarded by electrons in vacuum tubes; brain actions being detected by radio amplifying apparatus; human tissues being measured by electrical engineering methods to discover their "phase angle" under different conditions; gonorrhea cured by electrical heating methods which were developed for metallurgical uses; biological membranes partially simulated by chemically produced films.

I recall some ten years ago the late Dr. Augustus Trowbridge, then European Director for the Natural Sciences under the International Education Board, told me of his belief, based on study of work in many laboratories, that the next generation would witness a fundamental forward movement in the biological sciences comparable to that which came in the

physical sciences with the work of Faraday and Maxwell, or more recently with the discoveries of the electron, roentgen-rays, radioactivity and atomic transmutation. He said, furthermore, that he expected this advance in biology to come about through use of technics supplied from the sister sciences of physics and chemistry. Certainly the new developments of the intervening ten years go far in substantiation of this prophecy.

Admitting, therefore, the rapid advance of biological science and its opportunities to draw for assistance upon its sister sciences, the question arises, is there some step which we can now take that will facilitate and expedite this development? I believe that one clue to the answer to this question is found in two parallel situations: Very, very few biologists or physicians are trained in these technics of physics and chemistry, or have any understanding of the concepts and methods of these sciences which may be applicable in their own science; conversely very, very few physicists or chemists have any knowledge of the problems of biology. Neither speaks the other's language or thinks about his problems. So, I believe that one forward-looking step may be taken by the parallel training of young scientists in biology, physics and chemistry in a manner which I will suggest later.

Of course this is not a new idea. There are some biophysicists and some biochemists who are doing excellent work. And for many years the border lines between the biology and physics and biology and chemistry have been attacked. But these have been reconnaisance skermishes by raiding parties rather than a major engagement by an adequate and well equipped army. I know that most physicists who have gone into biophysics have gone in mainly as technicians, while most biologists in the same field have been fumbling with big ideas which they had not the background to handle effectively. Those few who have become first-rate biophysicists or biochemists have done so through unusual native ability and hard work, and not through adequate training.

Such considerations led a group of my colleagues, who were interested in attempting to devise an improved basic training for the fields of biophysics and biochemistry, to follow a suggestion derived from a somewhat analogous situation about 30 years ago—that time in the field of chemistry rather than biology. Then industrial chemistry was rapidly becoming important. Many successful exploratory developments had been carried out in applying methods and principles of physics and mechanical engineering to chemical manufacture. At that point, three men together devised a new type of training for young men preparing for the chemical manufacturing industry. Instead of cramming the minds of student chemists with a mass of descriptive detail as to how this product is manufactured, that product is manufactured, and so on, they concentrated their training on a limited number of processes and operations which were basic to all chemical manufacture, and gave a thorough grasp of these processes from the physical, chemical and mathematical viewpoints—all built upon thorough groundwork in these basic sciences. These unit operations were things like distillation, mixing,

drying, heat transfer, chemical reaction, transfer of fluids, etc. At one stroke this new concept brought order out of chaos in the chemical industries; their problems had been reduced to common terms; technical advance in one industry was immediately transferrable to other industries. In the short space of 30 years chemical engineering has become one of the most useful and vigorous of all the applied sciences.

Just as systematic applications of physics and mechanical engineering to chemistry produced a useful art of chemical engineering, so a systematic application to biology of physics, chemistry and electrical engineering may create a useful art of biological engineering. The choice of the name "biological engineering" is the result of much thought and consultation. The names biophysics and biochemistry are, neither of them, sufficiently inclusive, and their combination is clumsy. Biotechnology would be a good title. But the designation of biological engineering was suggested as appropriate because our objective so aptly conforms to the well known definition of engineering as "the art of organizing and directing men and of controlling the forces and materials of nature for the benefit of the human race." Within this conception lies ample scope for every activity from instrumentation to theory, from biophysics to biochemistry, so long as its objective is the marshalling of all available resources to aid biology for the benefit of humanity. When one of my colleagues first suggested this name to me, he said, "I know you don't like the name now, but it will grow on you as you think it over." He was right.

What, then, is the program for biological engineering, in order that it may fulfill its objective of systematically uniting physics, chemistry, mathematics and engineering to serve biology? As I see it, three features are essential: an educational program, a research program and an organization. Realizing that, if the program has merit, it will be improved by experience and further thought, nevertheless the following suggestions may be offered as a starting point.

Educational Program. The first consideration in planning an educational program is its objective and then its scope and subject matter. Here we may follow the analogy of chemical engineering, with its "unit processes" and "unit operations," and proceed to analyze our available concepts, tools, technics and opportunities, as follows:

Among the types of energy likely to be usable are the following: electromagnetic vibrations—infra-red, visible and ultraviolet light, roentgen-rays, radio frequencies; radioactivity; electricity; bombarding particles like electrons, protons or neutrons; supersonic vibrations; heat; chemical energy; magnetic fields; surface tension.

Among the ways in which these types of energy are likely to be involved are the following: stimulation of protoplasms; induced chemical changes in organic materials, living or once living; effects on enzyme action; therapy in disease; abiotic action on deleterious microörganisms; effects on hormones

and vitamins; spectroscopic analyses; roentgen-ray analyses of crystal structure or molecular aggregations; electrokinetics of cell membranes; electrophoresis of cells; tracer studies in metabolism and other physiological processes; mutations.

There will be required the construction and operation of devices for objective measurement of the changes induced as above, including measuring and recording of: temperature; pressure; humidity; air motion; gaseous relations; motion and time; amplification of feeble energies without distortion, by mechanical, thermionic or photronic devices; radiation measurements, as roentgen-ray dosages, radioactivity, cosmic ray counting, mitogenic radiations, spectrophotometry; hydrogen-ion concentrations; oxidation-reduction potentials; vapor pressures; heat flow and insulation thermodynamics; surface tension, conductance and impedance in protoplasms; diffusion and osmotic effects across membranes; molecular weights and isoelectric points; colloidal phenomena; agglutination and anti-body relations; electrical potentials, Donnan equilibria and Helmholtz double layer phenomena; axone potentials and action currents; reflex time and tropisms.

Among the technical skills useful in constructing experimental and recording apparatus the following are suggested: design and construction of amplifier circuits, transformers and meters; machine tool work and glass blowing; design and operation of vacuum pumps and pressure gauges; production of uniform or varying temperatures; design and operation of thermionic, photronic, vacuum and ionization tubes; photography and photometry; optical measurements; spectroscopy, absorption and emission spectra, absorption coefficients, use of glass, quartz and grating spectrometers; supersonic devices; radiation sources, electromagnetic, monochromatic, etc.; use of optical filters; microscopic technics, including transmitted and oblique illumination, dark field, quartz and lithium fluoride microscopes, ultramicroscopes; preparation and handling of pure gases; equipment for organic and inorganic chemical analyses; centrifuges.

Among the fields of usefulness of biological engineers may be listed: medical schools; hospitals; medical and biological institutes; universities; food companies, as packers, canners, bakers, shippers and dairy products; manufacturers of pharmaceutical instruments, chemicals or drugs; industrial hygiene activities; government laboratories, as agriculture, food, health and standards.

On the basis of this analysis, the next step is to devise an educational curriculum which will provide knowledge of biology and at the same time training in the principles and technics of the coöperating sciences as listed above. I believe that this curriculum should recognize first, that the field is too broad to be handled, even in an introductory manner, in a four year college course, and second, that education along these various lines should proceed more or less in parallel rather than ad seriatim.

This fact of "parallel" training is important. A student entering this field has hitherto been quite generally forced to specialize in one aspect, such

as chemistry or biology, and has then had to go back after graduation to pick up the remaining features of the combined program. As I have seen this attempted in a number of cases, I have been impressed with its poor psychological arrangement. But the curriculum which I shall describe makes progress possible at a more or less uniform level in the various fields. This has the advantage of breaking down the more or less artificial barriers between the different fields and of permitting a more unified conception and a more coördinated training.

Along these lines, therefore, the following curriculum of professional subjects has been approved by the faculty of the Massachusetts Institute of Technology for a course in Biological Engineering:

First year: general chemistry, physics and calculus, each through the year; engineering drawing and descriptive geometry each for a half year.

Second year: physics through the year, and a half year each of general chemistry, qualitative analysis, general biology, comparative anatomy, calculus and differential equations.

Ensuing summer: organic chemistry.

Third year: physical chemistry through the year, and a half year each of invertebrate zoölogy, bacteriology, physiology and electrical engineering.

Fourth year: a half year each of electrical engineering, biochemistry, biophysics, optics, atomic structure and some professional electives.

Fifth year: advanced bacteriology, colloid chemistry, biological engineering and thesis through the year, and a half year of zymology and some professional electives.

In addition to these professional subjects, the curriculum includes courses in English, history, modern language, economics and some elective general studies.

The professional electives are chosen in the fields of physics, chemistry, biology or engineering.

This five year course leads to a master's degree in biological engineering, but students with promise and ambition should be urged to proceed with at least two more years of graduate study to the doctorate.

Research Program. I believe that the best possible value in this field of biological engineering can only be attained if a research program and an educational program proceed side by side, each drawing strength and inspiration from the other. It is obviously not possible here to outline the scope and content of a research program, since this will vary greatly in accordance with the interests of the staff. You may be interested, however, in a very brief description of what we are now doing in this field at the Massachusetts Institute of Technology—not as a statement of an ideal, but rather as an illustration of the opportunities for coöperation between specialists in different departments drawn together around biological engineering as a coördinating influence. Associated in many aspects of this

work are also the Harvard Medical School, the Massachusetts General Hospital, the Lahey Clinic and other groups, for such a program must be essentially coöperative.

The technic of radioactivity measurement developed by Professor Evans has been combined with that of the metabolism of calcium and allied metals under Professor Aub to perfect a method for measurement and cure of radium poisoning. Similar radioactivity technics are being used in cooperation with Dr. Hertz working under Dr. Means to investigate iodine metabolism with some interesting therapeutic possibilities in view. Also this radioactive technic is being used to investigate phosphorus metabolism in the dentine and enamel of the teeth of humans and rodents, in the study of bone sarcoma, and other problems.

The high voltage electrostatic generator invented by Professor Van de Graaff is in successful use in a 1,200,000 volt roentgen-ray installation in the Huntington Memorial Hospital under Dr. Dresser, who recently reported the very promising clinical results on different types of cancer in the first six months of use. An improved model of this type of roentgen-ray outfit is now under construction in our electrical engineering laboratories for the Massachusetts General Hospital. The super voltage Van de Graaff generator, formerly installed on the estate of Colonel Green at Round Hill, has been moved to Cambridge and is being adapted for the production of large quantities of artificial radioactive materials, like sodium, iodine or phosphorus, for use in physiological and medical research.

The fundamental nature of the biological action of penetrating radiations is being investigated, starting with a very simple case—the bombardment of unicellular organisms by electrons of regulated speeds.

A series of organic peroxides has been discovered by Professor Milas, possessing biologically interesting properties. For example, they are unusually good bactericides and fungicides, and have yielded some remarkable results in the cure of athlete's foot and pyorrhea. Their mild oxidizing properties, and relative absence of deleterious action on tissues, suggests their possible beneficial action in diseases, like cancer and dementia praecox, which are characterized by low oxygen metabolism. Investigation of these possibilities is being undertaken in collaboration with Dr. Hoskins, Director of the Memorial Foundation for Neuro-Endocrine Research.

Coöperation of physicists with Professor Bunker has led to invention of a new method for activating ergosterol and also to a technic of monochromatic ultraviolet irradiation which has permitted a closer definition of the spectral range and efficiencies of antirachitic effects of ultraviolet light.

An automatic quantitative color analyzer, developed by Professor Hardy, is being used to separate the reddening of skin due to modified vascular action from true erythema produced by roentgen-rays and other agencies.

The carcinogenic properties of chemicals are being studied by a new method by Dr. Goldstein. He finds that those chemicals which will produce cancer in experimental animals after some months of application, will also

produce abnormal growths in bacteria in only a few hours. Thus far he has found complete agreement as to carcinogenic or noncarcinogenic properties of the various chemicals tried, and if this agreement is found to be general, the new bacterial test will greatly expedite the examination of other chemicals with respect to this property.

Utilization of facilities for upper atmosphere studies provided by our meteorological department has enabled Professor Proctor to develop some very interesting technics for investigating the distribution of microbes, pollens and fungus spores in the upper atmosphere and for studying their transport by air currents. Already some important results have been secured in such subjects as the spreading of gypsy moths by their larvae, and the dissemination of a serious fungus disease of wheat.

Many other examples might be added to these which I have purposely selected principally from the field of medicine. Others relate to food technology, industrial hygiene, etc. But let me give one more illustration which illustrates unusually well the possibilities of coöperation of specialists in different fields. I refer to a possible approach to the study of fatigue of automobile drivers.

Professor Horton, an electrical engineer, has developed a very accurate method for measuring the "phase angle" of living tissues. This phase angle expresses the relation between electrical reactance and electrical resistance. In addition to showing a correlation with certain glandular disorders, such as myxedema and Addison's disease, it now appears that the phase angle may be used as a quantitative measure of fatigue. This is not yet certainly established, but if it should be, then the following study of fatigue of automobile drivers would be possible.

The person under investigation will be seated on an automobile seat, with his hands on a steering wheel, and the whole outfit mounted on a shaking table devised by Professor Ruge for study of behavior of small model building structures in the accurately reproduced motion of earthquakes. This reproduced motion is secured by a hydro-electrical apparatus controlled by a beam of light passing through the irregular tooth-like edge of a rotating cam. This tooth-like edge is shaped to reproduce the earthquake motion in the shaking table, and the edge shape is calculated by means of the machine for mechanical solution of differential equations devised by Dean Bush and using earthquake data secured by a special type of seismograph built by Professor Slichter.

By driving any given type of automobile, equipped with such a seismograph, over any given type of road, and operating on this record with the differential analyzer to calculate the required cam shape to make the table shake just as did the automobile on the road, it is obvious that the driver may be given a "synthetic" ride to reproduce the jiggles and bumps of the real ride for any desired duration of time. He can be placed in a compartment like an actual automobile and air-conditioned to reproduce the temperature, stuffiness, carbon monoxide content, etc., of any given driving

conditions. By methods devised by Dr. De Silva of Harvard, he can even be given the synthetic job of driving in traffic.

All this time his phase angle, and hence his fatigue, is being recorded, his reaction time can be tested whenever desired, and any other tests may be made and automatically recorded.

If this should be done, we would have brought to bear on the study of fatigue, technics developed for other purposes by electrical, mechanical and civil engineers, a geologist, a physicist and a psychologist. Whether or not this will be done remains to be seen, but it illustrates the possibilities of cooperative effort.

Organization. Finally, as to organization, I should say that a department of biological engineering should be headed by a biologist, and should include a physicist, an organic chemist, an analytical chemist and an electrical engineer. There may be others. Then there should be coexistent departments in the scientific and engineering fields whose members can be drawn in for consultation and temporary help, when required, in their respective specialties. And there must be a coöperating medical group to handle medical aspects deriving from the program. Wherever such an organization can be set up, there I believe that what I have ventured to call " biological engineering " may serve a useful function in promoting the more effective marshalling of our existing knowledge in many fields for the specific objective of advancing our knowledge of biology and its applications to human welfare.

In conclusion, I would like to make one comment lest, in my effort to present the case for biological engineering, I may have given the impression that I believe the physical and engineering sciences can step blithely in to lead the biologists to the quick solution of their problems. I do not believe this at all; I only believe that there may be an opportunity now for us all to get together more effectively along some such line as I have tried to suggest. The main avenue of advance is, and will continue to be, the direct approach through biology, physiology and medicine. But these problems are so complex, so vast in scope and human import, that every promising avenue of approach to their solution should be followed. And I believe that this avenue of biological engineering shows some real promise of leading in the desired direction.

CASE REPORTS

SUBARACHNOID HEMORRHAGE FOLLOWING INJECTION OF EPINEPHRINE*

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Epinephrine is regarded as a harmless drug, the only common contraindications being angina pectoris and hypertension. Its use in the field of allergy is practically universal. Serious complications following its subcutaneous administration are not reported. Hence, we feel that the occurrence of a subarachnoid hemorrhage following the subcutaneous injection of 0.5 c.c. of epinephrine 1/1000 solution is of sufficient interest to be reported in detail.

Subarachnoid Hemorrhage

The recognition of subarachnoid hemorrhage as a clinical entity has been greatly simplified since the report of Symonds and Cushing [1] in 1923, dealing with intracranial aneurysm. Previous to this, the reports were largely pathological studies of cases that had not been diagnosed clinically. However, following this contribution, clinical reports [2] of cases recognized and properly treated during life began to appear in the literature.

Subarachnoid hemorrhage in young adults is by no means an uncommon occurrence. It has been reported as having occurred in some cases at rest, in others during coitus, straining at stool, physical exertion such as weight lifting, emotional upsets such as fright, etc., all of which elevate blood pressure. At times it has occurred during pregnancy, labor and several hours to several days postpartum.[3]

The underlying factor in this disease, miliary aneurysm, is most often found in one of the superficial cerebral arteries. In many younger individuals no lesion has been demonstrated at autopsy. Vascular syphilis, arteriosclerosis, infections such as subacute bacterial endocarditis, toxins and chronic alcoholism have been considered important etiological agents. Eppinger [4] in 1887 was the first to suggest a congenital defect in the vessel wall. Von Hofmann [5] in 1894 found the favorite site of aneurysm to be at the bifurcations of the cerebral vessels. Fearnsides [6] studied 5432 head examinations of 7924 autopsies and found 44 aneurysms. Forbus [7] studied the cerebral vessels of a case of subarachnoid hemorrhage. He found that there were multiple aneurysms arising only from vessels of the carotid system and that all were located at the points of bifurcation, with no evidence of inflammation but a definite defect in the muscularis at numerous points of division. No definite muscularis abnormality was demonstrated in the other arteries except at points of bifurcation. The location of the aneurysms corresponded exactly to the location of the muscularis defect. This led to the study of embryos in which he found that the

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muscularis of the arteries and that of their branches develop independently. Thus, it was hypothesized that the muscularis may not fuse at the point of bifurcation, leaving a defect. Forbus performed some interesting manometric experiments demonstrating the pressure effects on the points of bifurcation, concluding: "Our interpretation of the facts, as we have stated it in this account of multiple miliary aneurysm formation, forces us to the conclusion that multiple aneurysms of the superficial arteries of the brain, as well as those of the arteries of medium size of other organs, are acquired lesions based upon a congenital arterial structural imperfection, a defect in the muscular coat, characteristically located at points of bifurcation." Strauss et al.[21] found "arteriosclerosis of the cerebral arteries to be the most common pathologic condition responsible for the disorganization of the vessel wall, the aneurysmal formation, the rupture and the hemorrhage into the subarachnoid space, irrespective of the age of the patient."

Briefly, the history obtained in cases of spontaneous[8] subarachnoid hemorrhage is as follows: There is a sudden onset of intense, severe headache, which may be local or general, causing the patient to "hold the head with pain." It may originate in the back of the neck. A "feeling of something having snapped at the base of the skull" is sometimes described. Nausea and vomiting frequently accompany or follow the pain. At times the patient loses consciousness for a short period following which he may be drowsy and stuporous for varying lengths of time, sometimes going on to coma and death. Due to the blood present in the cerebrospinal fluid, acting as an irritant, there is neck pain and stiffness, Kernig's sign and a mild febrile reaction. Depending on the amount of blood and the location of the clot, there are various localizing signs. The eye grounds may show choked discs and hemorrhages. The pupils may be unequal, dilated or contracted. The pulse may be slow and the blood pressure elevated. Polyuria, glycosuria and albuminuria are encountered at times.

The diagnosis of subarachnoid hemorrhage is usually confirmed by the spinal fluid findings. Froin's observations[9] are still considered classical. The spinal fluid pressure is increased and in three successive fractions of fluid the blood is mixed to the same degree. The amount of blood and the color of the fluid vary. The supernatant fluid may be pale orange or brown to golden yellow. No coagulum forms in the fluid. In hemorrhage incident to spinal puncture the amount of blood decreases in the three fractions and coagulates in the fluid, the supernatant fluid is clear and colorless. In subarachnoid hemorrhage the characteristic features are an even admixture of red blood cells, xanthochromia, crenated red blood cells on microscopic examination and absence of coagulum.

In an analysis[10] of 105 cases of subarachnoid hemorrhage Strauss and Tarachow concluded that the prognosis is worse with generalized vascular disease and better where there is no clinically evident hypertension or arteriosclerosis. The older the patient, the worse is the prognosis even without evidence of vascular disease.

In addition to symptomatic and supportive measures drainage of the spinal canal should be done at regular intervals. Authors have varied in their recommendations regarding this procedure but, in general, drainage is usually resorted to until the fluid clears. Pressure readings should be made at each tap.

The course and duration of the illness depend upon the amount of bleeding,

its location and whether there are immediate recurrences. In cases of spontaneous subarachnoid hemorrhage in younger individuals the patient usually improves rapidly during the first week and recovers in three to six weeks.

Epinephrine

Epinephrine causes a rise in blood pressure due to its effect in producing arteriolar constriction. The height of the rise varies with the individual and the method of administration. By the intravenous route, it produces a marked elevation, intramuscularly, the reaction is less, and subcutaneously least of all. "Epinephrine is easily oxidized and when introduced into the circulation it is so rapidly destroyed that an effective concentration in the blood is maintained for only a brief period, hence its evanescent effect" according to Rogoff.[11]

In experimental animals the response of the pial arterioles to the local application of epinephrine is the same as that of arterioles in other parts of the body.[12] In other animal experiments [13] it was found that a rise in blood pressure can overcome epinephrine vasoconstriction within the head. These latter experiments also suggest that the drug increases the cerebral circulation. In isolated dogs' heads Bouckaert and Jourdan [14] found that epinephrine produced vasoconstriction when perfused through the arterial system. In a later paper,[14] these workers reported that they had injected strong doses of epinephrine into the general circulation of dogs and had found that the distensive action of the systemic hypertension overcomes the local vasoconstrictive action of the drug. They believed that the musculature of the cerebral arterial walls, excited to constriction by epinephrine, limits the distensive effect of the hypertension. Cachera and Fauvert [15] performed similar experiments on dogs and their results are in agreement with the work of Bouckaert and Jourdan.

Gibbs and his coworkers [16] found in their human subjects "an abrupt and great acceleration of blood flow" following intravenous injections of 0.1 to 0.2 c.c. of 1/1000 solution of epinephrine which was "sufficient to cause a sharp increase in blood pressure and impulse rate." They believed the increase in flow was secondary to the increase in systemic blood pressure. In other cases they used amounts (0.01 to 0.005 c.c.) which did not cause a rise in the blood pressure but in "each instance there was a moderate increase in flow."

It has been stated that no obvious systemic effect is produced in normal individuals after subcutaneous injection of epinephrine; it was believed that absorption from the subcutaneous tissues was so slow that destruction or neutralization kept pace with it.[17] However, in 10 normal males under basal metabolic conditions Blumgart [18] found an increase in the velocity of peripheral blood flow averaging 81 per cent, an increase in the speed of pulmonary circulation averaging 76 per cent, an increase in pulse rate of 12 to 24 beats and an increase in pulse pressure produced by a rise in systolic blood pressure and a fall of the diastolic pressure. He used 0.5 c.c. of 1/1000 solution of epinephrine subcutaneously. Moreover, Jensen [19] found similar blood pressure changes in 13 normal persons injected, using 0.5 to one c.c. of 1/1000 solution of epinephrine subcutaneously. The increase in systolic blood pressure varied from 15 to 85 mm. of mercury, the maximal being reached in 11 to 46 minutes. The immediate response varied from 8 mm. in 22 minutes to 38 mm. in 3½ minutes. In three cases the pressure suddenly increased. Kylin [20] used one milligram of epinephrine subcutaneously in normal individuals and found a blood pressure

rise of 15 to 20 mm. in one to two minutes. The maximal effect was produced in 5 to 10 minutes. Harman [21] injected 0.5 c.c. of 1/1000 solution of epinephrine subcutaneously into women with normal menstrual cycles and found no rise in blood pressure over 8 mm. nor in pulse rate over five beats per minute. Myers and King [22] injected 10 minims of 1/1000 solution of epinephrine subcutaneously into 10 normal, healthy, white women between the ages of 20 and 30. Four showed no change in systolic blood pressure, five gave an immediate rise of from 8 to 10 mm. of mercury, and in one the systolic blood pressure rose 15 mm. within eight minutes. In four the diastolic blood pressure fell 10 mm. within eight minutes, in six cases there was no essential immediate variation. The diastolic blood pressure in all these cases showed a tendency to a lower level during the period of observation. The pulse pressure varied accordingly, showing an average immediate increase of 10 mm. of mercury. The average increase in pulse rate was twelve beats per minute.

Case Report

Mrs. M. F. G., aged 20, a primipara, delivered by low forceps on July 24, 1937. Her puerperium was uneventful until she developed urticaria on August 6, 1937. Except for the occurrence of hives in her mother and brother the family history was inconsequential. The urticarial attack on August 6 was mild, the itching being relieved by calamine lotion and several ⅜ grain ephedrine sulphate capsules. On the morning of August 7, 1937, these lesions had almost entirely disappeared and there was no itching. That evening about 9 p.m. one of us (B. S.) was called to see her. At that time she had a severe attack of urticaria with very annoying pruritus. Almost the entire body was red and there were numerous typical urticarial lesions. Dermographia was elicited. An injection of 0.5 c.c. of 1/1000 solution of epinephrine was given subcutaneously. Within one-half hour the skin was clear and there was no itching. About 45 minutes after the injection she developed a sudden, severe headache which was generalized and increased in intensity during the next two hours. (On later questioning there was no sensation of anything snapping in her head.) About an hour and a half after the injection the patient was given 10 grains of aspirin and three grains of Seconal, which she vomited immediately. She became very restless and apprehensive, complaining bitterly of headache, and vomited again in about 20 minutes. An injection of ¼ grain of morphine sulphate was given hypodermically and she slept throughout the night and was drowsy all of the next day (August 8). She vomited several times during the day and was able to retain only a small amount of soft food, awakening at intervals, complaining of severe headache. On August 9 she was stuporous and listless but could be aroused, complained of weakness and severe headache, and soon fell asleep. Her orientation was good. Her temperature was 100.4° F, pulse 48 to 56. The blood pressure was 130 systolic and 80 diastolic. There was marked photophobia. In consultation, one of us (M. F.) found a very rigid neck, Kernig's sign, slight limitation of external rotation of both eyes, and equal, slightly dilated, reacting pupils. The patient was hospitalized with a provisional diagnosis of meningeal irritation, possibly infectious. On admission the blood and urine were essentially negative except for moderate secondary anemia. Spinal puncture was performed, the findings of which are listed in table 1. A diagnosis of subarachnoid hemorrhage, secondary to epinephrine injection, was made. Dr. R. G. Spurling concurred in the diagnosis. He found no fundal changes. In all, five spinal punctures were done (table 1). The patient improved rapidly and was discharged on August 18, 1937, with slight neck stiffness, moderate photophobia and definite weakness. One month after the onset of this illness she had made a complete recovery.

TABLE I

Record of Spinal Punctures

Date	Pressure in millimeters of spinal fluid	Color and amount of fluid withdrawn	Red blood cell count	White blood cell count	Differential count	Remarks
8/9	190	Very bloody. Bright red. Very cloudy. 25 c.c.	250,000	222	All poly's.	Supernatant fluid slightly xanthochromic B.P. 130/80
8/10	130	Bloody. Bright red (less than above). Cloudy. 20 c.c.	20,500	0–1	All poly's.	Increased xanthochromia B.P. 114/64
8/11	30	Light orange to amber. Cloudy. 15 c.c.	30,000	65	91% poly's. 9% lymph's.	Xanthochromic B.P. 110/60
8/13	110	Light amber. Slightly cloudy. 8 c.c	10,000	60	74% poly's. 25% lymph's. 1% mono.	Xanthochromic B.P. 120/80
8/16	110	Light amber. Very light cloud. 4 c.c.	35–40	8–10	96% lymph's. 4% poly's.	Xanthochromic

COMMENT

This case has many interesting features. Assuming that there actually existed a congenital aneurysm, how did it withstand the stress and strain of labor only two weeks previously? It is true that the second stage was considerably shortened by low forceps delivery yet at some time during labor there must have been some strain. It is possible that this exertion weakened the aneurysmal wall sufficiently so that the rise in blood pressure and the increase in cerebral circulation volume and velocity, after the injection of epinephrine, were able to cause its rupture. It is probable that this individual is unusually responsive to epinephrine and had a sudden, sharp rise in systemic blood pressure and marked distention of the cerebral arterial system. The possibility that some of the material injected entered the venous circulation cannot be overlooked.

A search of the literature has revealed no case of subarachnoid hemorrhage under similar circumstances. Symonds [23] writes: "I have not met with or heard of a similar case." We feel that the unusual circumstances associated with this accident warrant this report.

SUMMARY

Herein is reported an instance of subarachnoid hemorrhage in a young woman two weeks postpartum following an injection of 0.5 c.c. of 1/1000 solu-

tion of epinephrine subcutaneously. The modus operandi is suggested. The patient recovered.

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HEMOLYTIC STREPTOCOCCIC ANGINA WITH AGRANULOCYTOSIS TREATED WITH PRONTOSIL AND SULPHANILAMIDE*

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THE fundamental discovery by Domagk [1-4] of the protective action of certain sulphonamide derivatives of the azo dyes in experimental hemolytic streptococcic infection, and the supplementary demonstration by Tréfouel, Tréfouel, Nitti, and Bovet [5] of the similar action of para-aminobenzenesulphonamide, have received abundant confirmation.[6-13] From the date of Domagk's original publication [1] an ever increasing volume of clinical reports has been appearing in the current medical periodicals concerning the favorable influence of these chemotherapeutic agents in the treatment of the various types of hemolytic streptococcic infection. This literature has contained scattered references to the therapeutic results obtained in the treatment of acute pharyngitis, tonsillitis, and peritonsillar abscess.[14-19, 12, 20] Although a brief report on a similar case by Schur and Singer [21] has already appeared, the present report is the earliest detailed record of the clinical course and laboratory findings in the treatment with Prontosil and sulphanilamide of a fulminant necrosing pharyngitis accompanied by a complete agranulocytosis.

CASE REPORT

On September 2, 1936, A. McM., a white male, 52 years of age, suddenly developed sharp lightning-like pains with deep boring sensations in the shafts of the right and left femurs and along the crest of the left tibia. The pains, which were very severe and exhausting, did not appear to follow the course of either the femoral or sciatic nerve distribution. They recurred at frequent intervals over a period of several days.

On September 3 an indefinite soreness of the throat, with chilliness, a rapidly rising temperature, headache, and generalized body aches, confined the patient to bed.

On September 4 the patient was first seen by the physician. The muscle, joint, and bone aches, which were causing the most acute distress, were still the chief complaint. Four or five years previously the patient had been affected with some bone disease in the region of the right hip, for which an operation had been performed and a cast applied. But no tenderness was to be elicited on palpation or pressure over any of the affected bones. The throat soreness had increased and pain on swallowing had developed. The throat was very much reddened and inflamed, but no spots, patches, or areas of pseudo-membrane formation were visible. The tonsils had been

* Presented before the Staff Meeting of the Bay Ridge Hospital, Brooklyn, New York, May 4, 1937.

removed years before but some tissue fragments remained. The patient had suffered from several attacks of throat infection of ordinary severity during the preceding three years. The temperature was 101°.

The clinical picture was that of the usual septic sore throat. Treatment was instituted on this basis. The affected areas of the throat were painted with a 3 per cent solution of iodine in glycerin; an injection of a non-specific protein antigen was administered subcutaneously, and a mixture containing salicylates and gelsemium prescribed for internal medication; perborate of soda as a mouthwash and gargle, and cold compresses to be applied externally, were recommended. Against advice, but for reasons of economy, the physician was requested to return only on call.

Four days later, on September 8, the physician was called again. The pharynx, tonsillar areas, and uvula now showed one extended mass of grayish-black necrotic membrane. The patient was confused and drowsy. The bone pains had ceased and the body aches were less, but the headache, which was somewhat localized at the back of the neck, was worse. The breath was foul. The temperature was 107° F. by mouth. The injection of 10,000 units of diphtheria antitoxin, which was given immediately on the impression that a septic diphtheria had developed, was without effect.

On September 9 the throat smears and cultures, which had been sent to the laboratory, were reported to show a preponderance of streptococci of the hemolytic strain, as well as many other organisms, but no Klebs-Löffler bacilli, or fusiform bacilli and spirochetes. The white blood cell count and differential was reported to show only 1200 cells consisting entirely of lymphocytes with a complete absence of polymorphonuclears.

The final diagnosis, which was first made at this time, was therefore hemolytic streptococcic angina with a complicating agranulocytosis. There was no recent history of having taken any amidopyrine or related drug containing the pyrazalon nucleus. The prognosis was regarded as very grave.

By this time the patient was obviously critically ill. The skin was hot and flushed. The breath was very foul. Deglutition was practically impossible as fluids returned through the mouth and nose. Moderate swelling of the cervical nodes had taken place. The patient was stuporous, and the deep reflexes were greatly diminished. Yet examination of the heart and lungs was negative. The kidneys were functioning; the urine contained no albumin, sugar, casts, or pus.

Under these conditions the fight against this fulminating hemolytic streptococcic angina and the potentially fatal agranulocytosis was begun. Treatment was instituted under trained nurses in the home. After two days the patient was removed to the Methodist Episcopal Hospital in Brooklyn, New York. The statistics of agranulocytosis from all causes at this hospital, from 1928 to 1936, show in a series of 13 cases, 10 deaths and 3 recoveries.

Specific treatment was carried out on two lines: first, for the control of the hemolytic streptococcic infection, Prontosil and sulphanilamide; second, for the agranulocytosis, pentnucleotide and Liver Extract.

Prontosil solution was injected intramuscularly in 5 c.c. doses at four hour intervals five times in 24 hours. Sulphanilamide (Prontylin) tablets were crushed and given in watery suspension by means of a nasal tube in doses of 15 grains four times in every 24 hours.

Pentnucleotide was injected intramuscularly in 10 c.c. doses daily. Concentrated parenteral solutions of liver extract were injected intramuscularly in 3 c.c. doses twice on every other day.

Local treatment consisted of throat irrigations at two or three hour intervals with hot solutions of one-half per cent permanganate of potash alternating with weak solutions of perborate of soda or bicarbonate of soda.

Supportive treatment included a high fluid intake and frequent liquid feedings given by means of a Levine nasal tube, solutions of glucose intravenously, and $\frac{1}{60}$ of

a grain of strychnin arsenate and 3 minims of a 1:1000 solution of epinephrine chloride subcutaneously, twice or thrice daily. Intestinal elimination was aided by means of enemata.

In response to these measures a striking therapeutic result was obtained in combating the destructive pharyngeal infection and the total suppression of the granulocytes. This therapeutic result consisted in the subsidence of the toxemia, the healing of the throat lesion, and the concomitant regeneration of the polymorphonuclears. The remarkable reaction of the patient to the treatment was soon evident.

The maximum and minimum temperatures were appreciably lower on each succeeding day of treatment, and after the fourth day the temperature dropped sharply to normal (table 1, figure 1). The mental confusion and stupor lessened. The general condition of the patient improved.

TABLE I

Days from onset	Temperature		Leukocytes	Lymphocytes				Granulocytes										Monocytes	
	Maximum	Minimum		Large		Small		Premyelocytes		Myelocytes		Metamyelocytes		Neutrophiles		Basophiles			
			total number	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*	*per cent*	*number*
3	101																		
7	107		1,200	32	374	68	826												
8	104.3	101.8																	
9	104.8	102																	
10	103.6	103	2,100	24	504	76	1,596												
11	103.6	99.8	1,900	26	494	71	1,349							3	57				
12	102.6	98.6																	
13	100.6	98.6	4,500	15	675	53	2,380							31	1,395			1	45
14	100.6	100.2	9,100	9	819	46	4,186	3	273	6	546	7	637	29	2,639				
15	100.6	99	11,900	13	1,547	27	3,213	2	238	4	476	23	2,737	31	3,689				
16	100.6	99	16,000	8	1,280	17	2,720	2	320	5	800	33	5,280	35	5,600				
17	100.4	99.2	16,000	11	1,760	23	3,360			2	320	31	4,960	35	5,600				
18	100.4	99	15,628	7	1,152	9	1,480			1	165	36	5,922	42	6,931			5	822
19	100	99.4																	
20	99.6	98.8	17,550	4	702	6	1,053							90	15,795				
21	99	98	12,700	11	1,397	18	2,266							71	9,017				
22	98.6	98	9,850	9	887	15	1,477							76	7,486				
23	98.8	98	11,600	8	928	14	1,624							76	9,048	2	232		
24	98.6	98.6																	
25	98.8	98.2																	
26	98.6	98																	
45			6,400	4	256	49	3,136							47	3,008				

By the seventh day a decided change was evident in the condition of the throat. The offensive odor had disappeared. The thickness and tenacity of the membrane began to decrease, and a gradual exfoliation resulted.

From the time of the highest temperature when the blood was first examined the number of both the large and the small lymphocytes per cubic millimeter showed a gradually increasing upward trend. Granulocytes first reappeared in the blood between the second and the third day of treatment, or during the interval when the fever was slowly receding. Almost from the time of their reappearance the polymorphonuclear neutrophiles showed a rapidly increasing upward trend, but by the time when the temperature had reached normal were present in less than one-third their normal number (table 1, figure 1).

On September 14 the temperature rose abruptly to 100.6° where it remained practically constant for a day and a half. From then on it fluctuated consistently for several days between about 99° in the morning and 100.5° in the afternoon.

Duplicate blood cultures in broth were made at the onset of this secondary rise in temperature. One was negative. The other showed a slight delayed growth of hemolytic streptococci. Nevertheless the existence of a bacteremia was questioned.

Inasmuch as these streptococci proved to be of a short chain strain, unlike that isolated from the throat, they were felt to have been a contaminant.

With the secondary rise in temperature a slight increase in the number of large lymphocytes and a marked increase of small lymphocytes occurred. A brief spurt of premyelocytes, a prolonged wave of myelocytes, an increasing flood of metamyelocytes and polymorphonuclear neutrophiles and a final surge of monocytes also entered the blood. As a result, the leukopenia which remained after recovery from the agranulocytosis was replaced by a marked leukocytosis (table 1, figure 1).

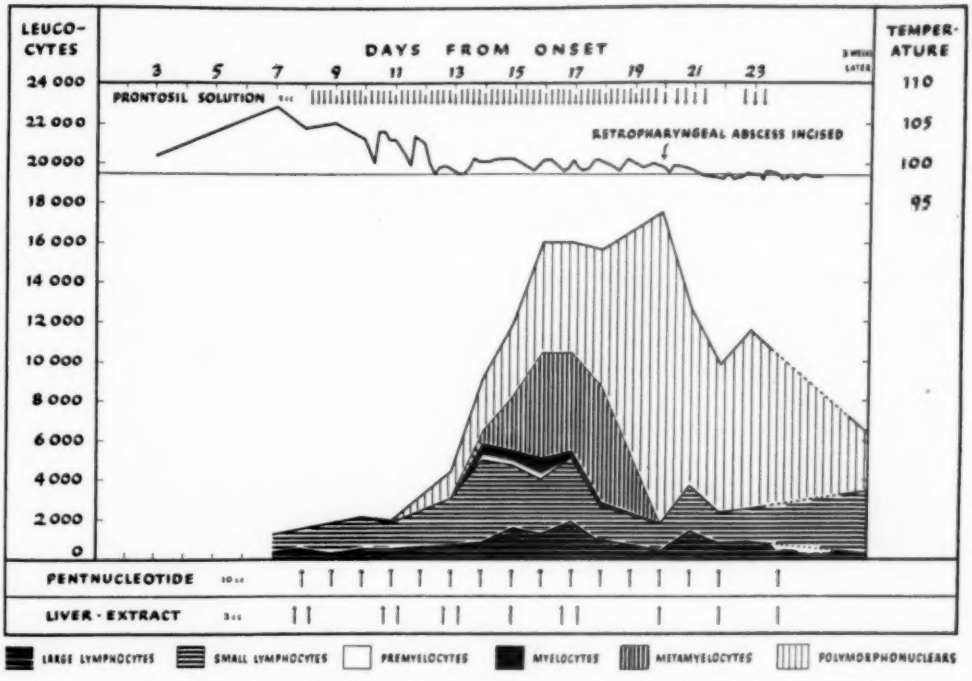

FIG. 1. Hemolytic streptococcic angina with agranulocytosis: temperature chart, blood picture, and medication.

During the development of this leukocytosis it was observed that most of the leukocytes showed pronounced toxic degenerative changes. On this account it seemed advisable, in view of the sustained fever which, at the time, could not be satisfactorily explained, to resort to a blood transfusion. On September 16 a transfusion of 300 c.c. of type IV blood was accordingly given.

On September 18 a tendency toward urinary retention developed which required the use of the catheter for several days.

This low grade fever proved to be the result of a large abscess which had formed in the retropharyngeal space. On September 21 the retropharyngeal abscess was opened and freely drained of a large amount of greenish-yellow pus. The next day the power to swallow returned in sufficient degree to permit of the discontinuance of the nasal tube. Following the drainage of the abscess the temperature rapidly approached normal and remained so for the remainder of the convalescent period as the patient went on to make a complete recovery.

The polymorphonuclear leukocytosis continued to increase up to the time when the retropharyngeal abscess was incised. The excess of neutrophiles in the blood then receded, rapidly at first, but more gradually later.

After September 21 the injections of Prontosil solution were reduced, first to three a day, then to three on every other day; of Pentnucleotide to one every other day; and of liver extract to one every second or third day.

On September 28 all medication was discontinued, and the patient was discharged from the hospital.

During the period of the absolute agranulocytosis the red cell count was 4,800,000, the hemoglobin 66 per cent, and the color index 0.69. The blood platelets maintained a count of between 150,000 and 200,000 throughout the illness. After the final subsidence of the fever the red cell count at 4,200,000 and the hemoglobin at 65 per cent were only slightly below normal levels. Repression of blood cell formation in the bone marrow was evidently confined entirely to the granulocytes.

Subsequent to recovery a complete blood examination showed a white cell count of 6,400 leukocytes divided about equally between 3,000 granulocytes and 3,400 lymphocytes, a red cell count of 3,900,000 (table 1, figure 1), hemoglobin 73 per cent, and a color index of 0.93. The fact that there was a relatively high number of lymphocytes and a relatively low number of neutrophiles in the blood following recovery might suggest the presence of some degree of deficiency in the formation of the granulocytes.

In this case Prontosil and sulphanilamide evidently exerted a definite and specific action against the hemolytic streptococcic angina with a resulting suppression and elimination of the toxic focus that was causing the arrest of the maturation of the myeloblastic cells in the bone marrow. As soon as the production by the hemolytic streptococci of the toxins, which had a selected action against the leukocytes of the granulocytic series, was checked, time was permitted for the regeneration of the polymorphonuclears and the repair of the local damage sustained by the pharyngeal structures. The restoration of the maturation of the myeloblastic cells was, in all probability, abetted through their stimulation by Pentnucleotide and liver extract.

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RARE SEQUELAE OF PNEUMONIA; SUBCUTANEOUS, INTRAMUSCULAR AND RENAL ABSCESSES CAUSED BY TYPE XIV PNEUMOCOCCUS*

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The pneumococcus is seldom regarded as the cause of either skin or kidney lesions yet a few reports of such occurrences have been published. A number of observers describe the appearance of non-specific skin eruptions during pneumonia,[1] but others record the actual isolation of pneumococci from the lesions.[2] Mann and Gerboth [2] recovered pneumococci from a nodular eruption on the legs. Wakefield's patient with type II pneumococcic pneumonia developed intramuscular abscesses in the deltoid region and on the thigh. Schmidt-LaBaume and Otto noted vesicular lesions on the skin and mucous membranes from which pneumococci were isolated. Subcutaneous abscesses were noted in two of Preble's [3] patients. Finland [3] recorded 10 cases of subcutaneous abscesses caused by pneumococci but not associated with pneumonia; three were caused by type III pneumococci, two each by types II and XI, and one each by types VII, VIII, and XIV.

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Urinary tract infection associated with or caused by pneumococci appeared to be equally uncommon until the recent report of Moor and Brown [4] who found pneumococci of type XIV in the urine of an amazingly high proportion of patients. Practically none of the previous observers have even recorded the pneumococcus as the causative organism of urinary tract infections, yet in many cases the bacteria found have merely been entered as "cocci" in their statistical tables. Complete identification has seldom been made. Actual renal pneumococcus infection during or after pneumonia is very uncommon. Fahr [5] observed two instances with multiple renal abscesses and Reimann [6] reported a case with multiple kidney abscesses caused by type III pneumococci.

In the following case multiple subcutaneous, intramuscular, and renal abscesses were observed following type XIV pneumococcus pneumonia.

Case Report

History. A colored man, aged 27, was admitted to the medical service of Dr. H. A. Reimann, four days after the onset of type XIV pneumococcus pneumonia which followed a cold. The right lower lobe was consolidated and a friction rub was present. Vomiting and diarrhea occurred early in the course and the patient appeared to be very ill. A blood culture was sterile. The blood Wassermann reaction was positive. The temperature after admission to the hospital reached 40° C. (104° F.) during the remainder of the first week of illness, then gradually declined and became normal on the fourteenth day. On the fifteenth day the temperature rose to 38.4° C. (101° F.) and an abscess was noted over the sacrum which was incised and drained two days later. The pus contained a pure culture of type XIV pneumococci. The temperature thereafter fluctuated irregularly between normal and 39.1° C. (102° F.) for the rest of the observation period. Another abscess, 2.5 cm. in diameter also containing type XIV pneumococci in pure culture appeared two weeks later in the anterior abdominal wall. At the same time pain and tenderness were noted in the left interscapular region. A few days later a swollen, tender area 8 cm. by 4 cm. developed. Pus was aspirated. The abscess burrowed and spread under the muscle layers and skin to the right interscapular and cervical region. Upon deep incision and drainage 240 c.c. of thick pus were obtained from which type XIV pneumococci were isolated. The wound healed after a week.

The patient did not recover satisfactorily, the temperature reached fever levels daily and pyuria was noted on the forty-eighth day of illness. Type XIV pneumococci were recovered from the urine on several occasions but two blood cultures were negative. Examination of the abdomen revealed a large tender mass on the left side and a vaguely palpable mass on the right. A diagnosis of pneumococcus pyelonephritis was made. The leukocytes hovered between 11,000 and 20,000 per cu. mm. The blood urea nitrogen was 14 mg. per 100 c.c. The non-protein nitrogen rose progressively from normal to high levels and measured 111 mg. shortly before death. The urea clearance test a month after pyuria appeared was 44 per cent of normal, and after two months, 33 per cent of normal. Because of the evidence of increasing retention, left nephrostomy was performed by Dr. T. Fetter on the eighty-second day. Congenital polycystic kidneys with multiple abscesses were found. Drainage was maintained, but the patient became progressively worse and died four months after the onset of the pneumonia.

Necropsy performed by Dr. B. L. Crawford revealed that the lung lesion had healed. Chief interest focused on the enormous kidneys which weighed approximately 1700 gm. each and measured about 26 by 11 by 8 cm. The organs were composed of multiple cysts filled with pus and blood and no normal kidney structure was seen grossly. The chief pathologic diagnosis was polycystic kidneys, and suppurative nephritis.

Summary

A case of type XIV pneumococcus pneumonia was observed in which multiple subcutaneous and intramuscular abscesses, and renal abscesses superimposed on polycystic kidneys, occurred as sequelae. Type XIV pneumococcus is known to be especially invasive and the renal infection was assumed to be the result of infection of congenitally abnormal organs which seem to be especially vulnerable. There is also a probability that syphilis played a rôle in reducing the patient's resistance to pneumococcus invasion. It is of further interest to speculate on the peculiar affinity of type XIV pneumococci for the urinary tract as suggested by the studies of Moor and Brown.

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EDITORIAL

SHOULD LOBAR PNEUMONIA BE TREATED IN A HOSPITAL?

No question arising frequently in the daily practice of medicine involves more factors. It may be of interest to consider some of them in the light of present day methods in the treatment of the disease.

The facilities which are available in the home are naturally a first consideration. In impoverished patients the lack of such essentials as an adequate room, heat, light and equipment may at once settle the question in favor of the hospital, provided a well equipped hospital is within reach. Where the home can provide a suitable room and minimum equipment one must consider further matters.

What can be done in the home, for instance, to provide 24 hour nursing service? If graduate nurses are to be available this question is settled; but if they cannot, then probably special nurses could not be provided in the hospital for the same economic reasons.

Most private pavilions do not provide sufficient floor nurses to give adequate care and supervision to a pneumonia patient secluded in a private room. The patient usually fares better in these respects on the wards. The better type of practical nurses, or even intelligent strong women relatives will furnish closer supervision of the patient and better minor nursing care in the home than can be furnished to the patient on " floor care " by either ward or private pavilion. On the other hand in such important matters as hypodermic medication, proper recording of pulse and temperature and assisting the physician in giving serum, oxygen, etc., and reporting on the patient's condition, the partially trained nurse is often inadequate.

When matters are closely balanced between home and hospital as to nursing care, other considerations will decide the issue. The first of these, of course, is the matter of typing, cultures and serum administration. The hospital has strong practical advantages in all these respects. In fact in many instances it may be said that adequate use of these important aids to diagnosis, prognosis and efficient therapy is impossible in the home. On the other hand, given a home not too far from a modern laboratory and an energetic physician trained in the technic of serum administration, it becomes quite possible to give the patient in the home every advantage in this respect afforded by a hospital.

The use of oxygen therapy is likewise quite feasible in the home if the home is within range of one of the commercial houses which rent and service oxygen tents. Its efficient use, however, depends largely upon the quality of the nursing care available and upon the experience of the doctor in the supervision of this form of treatment. Moreover the expense of such oxygen therapy is often prohibitively great when provided in the home; whereas hospitals are apt to be more lenient in this respect.

A very important further point is the closeness of the physician's office to the home of the patient and the amount of time he can devote to the care of the patient. The task of caring for a case of pneumonia outside the hospital in a manner comparable to the routine of a good institution is not one to be undertaken by a man already heavily burdened with other very ill patients. Unless time can be given to the details of serum administration, for instance, its hazards will be notably increased. In considering this problem, however, the physician may well look realistically at the character of the professional care which can be furnished by the best available hospital. There may be no real benefit gained in this respect by placing the patient in a hospital which has no intern staff or in which the dependability of the house staff leaves much to be desired.

There are complications of pneumonia which may greatly add to the difficulties of home treatment: retention of urine, persistent vomiting, severe abdominal distention, certain types of delirium. There are others which may demand surgical intervention such as empyema, purulent pericarditis, or pneumococcic arthritis.

The problem of transportation to the hospital will often be an important one. Distance, roads, weather and the type of ambulance available must be given thought. In general, pneumonia cases stand transportation for reasonable distances in a good ambulance quite well during the first two or three days of their illness, but in the later stages of the disease such a move is a real handicap and may prove an immediate hazard.

The economic side should be considered by the physician only in this far. He owes it to the family to estimate for them, when asked, what the best treatment will cost in either place. It is their problem to determine what funds they can raise, the physician's to see that such funds are spent to the best advantage of the patient.

It is certain that the part of wisdom for the physician is to consider these and other individual factors carefully before coming to his decision. The decision should, however, be reached early and adhered to. There should be no moving of the patient late in the disease and because he is doing badly. The battle should be fought out in the home or in the hospital as seems best in the individual instance.

REVIEWS

Injection Treatment of Hernia. By CARL O. RICE, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; with the assistance and coöperation of HAMLIN MATTSON, M.D. 266 pages; 14.5 × 23 cm. F. A. Davis Company, Philadelphia. 1937. Price, $4.50.

Velpeau, in 1835, observed the accidental curing of a hernia, following the injection of a hydrocele with an iodine solution. He is given credit as the first physician to treat hernia by the injection method. Jaynes, in 1832, injected essential oils to cure hernia, and probably deserves priority. Dr. Ignatz Mayer, of Detroit, is credited with modernizing the injection treatment of hernia. He reported 2100 cases, from 1927 to 1932, with 98 per cent successful results.

The authors feel that ready acceptance of this method has been impeded, because of confusion with the injection of paraffin, and because at times charlatans and unlicensed practitioners have attempted it. The clinical aspects of the book are based on experience as obtained in the Hernia Clinic of the Minneapolis General Hospital, and in private practice. A detailed classification of hernias, anatomical relationships, and etiological factors are discussed. The importance of differential diagnosis is emphasized. A suitably fitting truss is considered mandatory for the cure of a hernia by this method. Suggestions for the selection and fitting of a truss are given. The comparative merits of various sclerosing solutions are described, along with a detailed technic of injection. Indications, contra-indications, complications and sequelae are discussed. The literature is reviewed and a comparison is made with the surgical treatment of hernia. A chapter is devoted to the histopathology of the injection treatment, in which the response of tissue to sclerosing solutions is demonstrated.

The final chapter is devoted to the medico-legal aspects of hernia, with a review of the various state laws.

It is a valuable contribution for those interested in the problem of the treatment of hernia.

G. H. Y.

Principles and Practice of Medicine. By SIR WILLIAM OSLER, M.D., F.R.C.P., F.R.S.; revised by HENRY A. CHRISTIAN, M.D., LL.D., S.D., F.R.C.P. Thirteenth Edition. 1424 pages; 17 × 25 cm. D. Appleton-Century Company, New York and London. 1938. Price, $9.00.

The thirteenth edition of this time-honored textbook of medicine has been revised by Dr. Henry A. Christian who in the preface assumes "responsibility for all changes and additions not credited by name to some other. . . ." In so doing Dr. Christian has given the book a conservative and sound uniformity of style which is lacking in some other texts. More than 200 pages have been added. Typhoid fever has been displaced from its leading position in favor of the more common pneumococcic infections.

The sections on deficiency diseases, blood forming organs and diseases of the circulatory system have been rearranged and brought up to date. Cinchophen has been included as a cause of toxic jaundice, and the discussion of arthritis has been lengthened and improved. New sections on lipid metabolism and on von Gierke's disease have been added.

There is a good discussion on protamine zinc insulin, but no mention is made of those cases in which, for various reasons, it must be discontinued. Lobectomy is recommended in the treatment of bronchiectasis. In sharp contrast to this vigorous

therapy, the ridiculously small dose of 2 to 4 c.c. of paraldehyde is advised in the treatment of delirium tremens. The precedent of former editors in not mentioning the psychoses has been followed. To the reviewer, this seems a mistake.

Dr. Christian is to be congratulated on the many improvements which he has made. It may be hoped that his assumption of the editorship of this text will restore much of its lost popularity. The book is recommended for use by both student and practitioner.

L. P. G.

Pathology of the Central Nervous System. By CYRIL B. COURVILLE, M.D. 344 pages, 17 × 25.5 cm. Pacific Press Publishing Association, Mountain View, California. 1937. Price, $5.75.

This book was written for the use of students and the general reader. It is based on a study of some 15,000 autopsies done in a general hospital, and therefore represents a good cross section of diseases of the nervous system that might be encountered in any large general hospital. The introductory chapter deals in some detail with the histologic alterations occurring in the parenchyma and interstitial elements of the nervous system. From this point on the reader is not burdened with too much histologic detail. The main emphasis is on the "development, gross appearance, and ultimate fate" of the common lesions of the nervous system.

The author has succeeded in injecting enough clinical correlation to give the general reader proper perspective of the subject. The text is well organized and follows the usual plan found in most texts on the subject. The appendix consists of eleven pages of clinicopathologic aphorisms which the author has written as an aid in the clinical diagnosis of nervous diseases. The following is an example of one: "The relatively rapid development of a paraplegia with signs of inflammation (fever, leucocytosis, etc.) often indicates an extradural spinal abscess. Immediate surgical exploration is indicated if the patient is to be saved."

The text is well illustrated with two hundred photographs and drawings. The type is very readable and the book has been nicely prepared. It can be recommended to any reader desiring general pathologic information on the common diseases of the brain and spinal cord.

J. G. A., JR.

COLLEGE NEWS NOTES

New Life Members

Announcement is made of the following additional Life Members of the American College of Physicians:

Dr. Eben C. Hill, Baltimore, Md.
Dr. James H. Means, Boston, Mass.

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—Supplement to Gutman's Modern Drug Encyclopedia, Fourth, Second Series;
Dr. Winthrop Wetherbee, Jr. (Associate), Boston, Mass.—1 book, "Medicine in the Outpatient Department";
Dr. Miles J. Breuer, F.A.C.P., Lincoln, Nebr.—1 reprint;
Dr. Coyne H. Campbell (Associate), Oklahoma City, Okla.—5 reprints;
Dr. Harry Halprin, F.A.C.P., Caldwell, N. J.—1 reprint;
Dr. D. O. N. Lindberg, F.A.C.P., Dectaur, Ill.—1 reprint;
Dr. James R. Lisa, F.A.C.P., New York, N. Y.—14 reprints;
Dr. Harold C. Lueth (Associate), Evanston, Ill.—11 reprints;
Dr. Wm. deB. MacNider, F.A.C.P., Chapel Hill, N. C.—4 reprints;
Dr. John I. Marker, F.A.C.P., Davenport, Iowa—1 reprint;
Dr. Samuel S. Paley (Associate), New York, N. Y.—3 reprints;
Dr. Samuel A. Shelburne, F.A.C.P., Dallas, Texas—2 reprints.

Committee on Nominations

President William J. Kerr on November 14, 1938, announced the appointment of Dr. Donald J. Frick, of Los Angeles, Calif., as a member of the Committee on Nominations to take the place of the late Dr. Walter P. Bliss, of Pasadena, Calif. Dr. Frick is an appointment from the Fellowship-at-large. The other members of the Committee consist of:

Dr. James Alex. Miller, New York City, *Chairman* (from the Board of Regents)
Dr. D. Sclater Lewis, Montreal (from the Board of Regents)
Dr. Henry M. Thomas, Jr., Baltimore (from the Board of Governors)
Dr. Fred W. Wilkerson, Montgomery, Ala. (from the Board of Governors)

Maryland Chapter of the American College of Physicians Holds Meeting, November 19, 1938

One of the largest and most successful State meetings of Fellows and Associates of the American College of Physicians was held at Baltimore, November 19, 1938, with Dr. Henry M. Thomas, Jr., Governor for Maryland, presiding. Dr. Sydney R. Miller, ex-President and Regent of the College, took an active part in organizing the program, and at the dinner which followed the afternoon session he addressed the group on topics of especial interest concerning the present and future activities of the College. The scientific program follows:

1. Teratoma of the Mediastinum. Surgical Treatment. William F. Rienhoff, Jr.
2. Regression of Retinitis in a Case of Arterial Hypertension. James Bordley, III.
3. Parietal Lobe Syndrome with Motor Aphasia with Autopsy Findings. Wendall Muncie.
4. Lymphoblastoma Simulating Hodgkin's Disease. Henry M. Thomas, Jr.
5. A Case of Malta Fever. Charles W. Wainwright.
6. Addison's Disease. Treatment with Desoxy-Corticosterone Acetate. George Thorn.
7. Type III Pneumonia. Three Cases Treated with Anti-Pneumococcus Rabbit Serum. Carmichael Tilghman.

Under the Presidency of Dr. James Alex. Miller, F.A.C.P., the New York Academy of Medicine conducted its Eleventh Annual GRADUATE FORTNIGHT, October 24–November 4, 1938. These meetings have become popular as concentrated postgraduate courses for physicians not only in the area of New York City, but from more distant points.

Dr. Charles F. Tenney, F.A.C.P. and Governor of the College for Eastern New York, and Dr. Mahlon Ashford, F.A.C.P., acted as Chairman and Secretary, respectively, of the Graduate Fortnight Committee. Among other members of the Committee were Dr. Thomas T. Mackie, F.A.C.P., Dr. Herman O. Mosenthal, F.A.C.P., and Dr. Bernard S. Oppenheimer, F.A.C.P. Dr. Mackie also acted as the Chairman of the Committee on Clinics.

The Fortnight was given over particularly to the subject of diseases of the blood and blood-forming organs. Among invited guests were Dr. George R. Minot, F.A.C.P., Professor of Medicine at Harvard University; Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine at the University of Michigan Medical School; Dr. Russell L. Haden, F.A.C.P., Chief of the Medical Division of the Cleveland Clinic; and Dr. Claude E. Forkner, F.A.C.P., Assistant Professor of Clinical Medicine at Cornell University Medical College. Fellows and Associates of the College filled thirty-nine different appointments on the program.

Sectional Meeting, Southern Illinois District, American College of Physicians

This year the annual meeting of the Fellows and Associates of the College from southern Illinois was combined with the Sixty-fourth Semi-Annual Meeting of the District Medical Society of Central Illinois, and was held at Decatur, November 15, 1938.

The meeting began at seven-thirty in the morning with a number of selected surgical clinics followed by a clinico-pathological conference and a tumor conference. The Decatur and Macon County Hospital provided a complimentary luncheon, after which the meeting adjourned to the Macon County Tuberculosis Sanatorium, where a motion picture, "Let My People Live," was shown.

The program from two o'clock in the afternoon on was sponsored especially by Fellows of the College and consisted of the following:

"Complications and Sequelae of Coronary Occlusion"—Dean F. Stanley (Associate), Decatur. Discussion: Dr. Edgar M. Stevenson, F.A.C.P., Bloomington.

"Paget's Disease"—Dr. M. E. Rose (Associate), Decatur. Discussion: Dr. Harold Swanberg, F.A.C.P., Quincy.

"Subdural Hematoma"—Dr. O. O. Stanley, F.A.C.P., Decatur. Discussion: Dr. George Parker, F.A.C.P., Peoria.
"Undulant Fever"—Dr. C. M. Jack, F.A.C.P., Decatur. Discussion: Dr. Warner H. Newcomb, F.A.C.P., Jacksonville.
"Diagnostic Procedures in Tuberculosis"—Motion Picture.
"Pulmonary Tuberculosis—Demonstrations"—Dr. D. O. N. Lindberg, F.A.C.P., Decatur. Discussion: Dr. Robinson Bosworth, F.A.C.P., East St. Louis.

In the evening there was a social gathering, and informal reception by the Macon County Medical Society, and dinner at the Hotel Orlando. The address of the evening, "The Challenge to American Medicine," was delivered by Dr. James D. Bruce, F.A.C.P. and Regent of the College, Vice President in Charge of Postgraduate Education, University of Michigan.

Sectional Meeting, Rhode Island Members of the College

One of the largest gatherings of medical men in Rhode Island was held at the Memorial Hospital, Pawtucket, in connection with Interne Alumni Clinic Day under the Chairmanship of Dr. John F. Kenney, F.A.C.P.

Clinics by the staff were given in the morning and were attended by all the Rhode Island Fellows and Associates. The afternoon program was turned over to the following members of the College:

"Coronary Insufficiency"—Dr. William D. Stroud, F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine.
"Endocrine Therapy in the Treatment of Allergic Disorders"—Dr. Harry Bond Wilmer, F.A.C.P., Assistant Professor of Clinical Immunology, University of Pennsylvania Graduate School of Medicine.
"Acute Hepatic Cellular Disease"—Dr. George Morris Piersol, F.A.C.P., Vice Dean for Medicine, University of Pennsylvania Graduate School of Medicine.

Included also on the afternoon program was Dr. Alexander Randall, Medical Professor of Urology, University of Pennsylvania and the title of his speech was "Obstructive Uropathy."

Under the Presidency of Dr. Elliott P. Joslin, F.A.C.P., Clinical Professor of Medicine, Emeritus, Harvard Medical School, and Medical Director of the George F. Baker Clinic, New England Deaconess Hospital, the Inter-State Postgraduate Medical Association of North America held its Twenty-third Assembly in Philadelphia, October 31—November 4, 1938.

Among contributions to the program by *Fellows* of the College were the following:

Diagnostic Clinic: "Acute Coronary Occlusion"—Dr. G. Harlan Wells, Philadelphia, Pa.
Diagnostic Clinic: "The Significance of Jaundice"—Dr. Henry A. Christian, Boston, Mass.
Diagnostic Clinic: "The Treatment of Anemia"—Dr. Russell L. Haden, Cleveland, Ohio.
Address: "The Therapeutic Value of Blood Transfusions"—Dr. Cyrus C. Sturgis, Ann Arbor, Mich.

Address: "Obscure Fevers as Diagnostic Problems"—Dr. George Blumer, New Haven, Conn.
Diagnostic Clinic: "Diagnostic Significance of Pain"—Dr. Frederick J. Kalteyer (Associate), Philadelphia, Pa.
Therapeutic Clinic: "The Treatment of Dehydration and Edema"—Dr. James H. Means, Boston, Mass.
Address: "Immediate and Ultimate Prognosis in Heart Disease"—Dr. Paul D. White, Boston, Mass.
Address: "Diagnosis and Treatment of Bronchogenic Carcinoma"—Dr. Arthur C. Christie, Washington, D. C.
Diagnostic Clinic: "Diabetes Mellitus from an Endocrinological Viewpoint"—Dr. Elliott P. Joslin, Boston, Mass.
Address: "A Medical Appraisal of the Surgery of Pulmonary Tuberculosis"—Dr. William S. Middleton, Madison, Wis.
Diagnostic Clinic: "Non-Organic Disorders of the Digestive Tract"—Dr. Alfred Stengel (Master), Philadelphia, Pa.
Diagnostic Clinic: "Somatic Complaints in the Neuroses; Case Presentations"—Dr. Peter T. Bohan, Kansas City, Mo.
Diagnostic Clinic: "Hodgkin's Disease"—Dr. Warfield T. Longcope, Baltimore, Md.
Address: "The Object and the Value of Preoperative and Postoperative X-Ray Treatment in Carcinoma of the Breast"—Dr. George E. Pfahler, Philadelphia, Pa.
Address: "The Prognosis and Treatment of Rheumatic Heart Disease"—Dr. Fred M. Smith, Iowa City, Iowa.
Address: "Pellagra"—Dr. John H. Musser, New Orleans, La.
Diagnostic Clinic: "Carcinoma of the Larynx with Special Reference to End Results"—Dr. Louis H. Clerf, Philadelphia, Pa.
Diagnostic Clinic: "The Differential Diagnosis of Diseases of the Chest and Abdomen"—Dr. David Riesman, Philadelphia, Pa.
Address: "The Present Status of Our Knowledge of the Suprarenal Cortical Hormone"—Dr. George A. Harrop, New Brunswick, N. J.
Address: "Studies in Growth—Precocious and Malignant"—Dr. Leonard G. Rowntree, Philadelphia, Pa.
Address: "Influenzal Pneumonias: Observations on Their Pathological Features and Clinical Characteristics"—Dr. Robert G. Torrey, Philadelphia, Pa.

Dr. Edward L. Bortz, F.A.C.P. and Governor of the College for Eastern Pennsylvania, Philadelphia, was elected November 16 as President-Elect of the Philadelphia County Medical Society.

Analysis of Circulation, "Annals of Internal Medicine"

The Executive Offices of the College recently completed a detailed analysis of the circulation of the Annals of Internal Medicine, using the circulation of the June, 1938, issue. The circulation of the Annals is not restricted to members of the American College of Physicians alone, but goes to many other physicians and institutions.

For the interest of members of the College, the following specialty and regional analyses are reproduced:

Specialty Analysis

(Volume XI, No. 12)

	Primary Specialty	*Secondary Specialty*
Internal Medicine	2,518	54
Allergy	10	116
Arthritis	5	40
Aviation and Military Medicine	8	17
Cardiology	56	398
Diseases of the Chest	49	122
Endocrinology	7	51
Gastro-enterology	43	208
Hematology and Blood Diseases	3	20
Immunology and Preventive Medicine	7	12
Medical Education and Administration	22	23
Metabolic Diseases	11	112
Physical Therapy	..	16
Research	8	39
Tropical Medicine	5	23
Tuberculosis	80	94
Total sub-specialties	314	1,291
Total, Internal Medicine	2,832	1,345
General Medicine	457	31
Neurology and Psychiatry	191	128
Medical Libraries and Societies	164	....
Hospitals	148	....
Pediatrics	145	21
Pathology, Clinical Pathology	133	93
Radiology, Roentgenology	97	23
Editors and Publishers	69	....
Medical Manufacturers	41	....
Dermatology, Syphilology	38	38
Public Health, Student Health	38	18
Surgical Specialties	33	8
Miscellaneous	95	48
No Secondary Specialty Given	....	2,728
	4,481	4,481

Regional Analysis

(Volume XI, No. 12)

Middle Atlantic States	1,609
Central States	1,176
Southern States	610
Western States	492
New England States	329
U. S. Possessions	49
Total, United States	4,265
Canada	95
Europe	57
Asia	23
South America	16
Mexico	7
Other Countries	18
	4,481

Dr. Herman M. Baker, F.A.C.P., Evansville, President of the Indiana State Medical Association, has appointed a committee to study the present national situation relating to the future practice of medicine.

Dr. Roscoe H. Beeson, F.A.C.P., Muncie, is among the appointees.

Construction recently was started on a new five-story, southern colonial style medical building at the University of North Carolina in Chapel Hill. Administrative offices, the division of public health, departments of anatomy, biologic chemistry, pathology, pharmacology, physiology, bacteriology, public health, and laboratories, seminar rooms and a large library will be housed herein. Dr. William deB. MacNider, F.A.C.P., is the Dean of the Medical School.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was recently installed as President of the American Congress on Physical Therapy.

Dr. Thomas Parran, F.A.C.P., Surgeon-General of the U. S. Public Health Service, was one of the principal speakers at the dedication exercises for a new library building of Abbott Laboratories, pharmaceutical manufacturers, in North Chicago, Ill., October 7. The dedication of this building marked the fiftieth anniversary of this organization.

Dr. Burton R. Corbus, F.A.C.P., Grand Rapids, Mich., was made President-Elect of the Michigan State Medical Society at its last annual meeting.

Dr. Henry A. Luce, F.A.C.P., Detroit, Mich., was installed as President.

The Michigan State Medical Society has initiated annual convocations for certification in graduate education. The first convocation was held during September, and was established to certify those physicians who attended special sessions in graduate education for four years. Physicians who complete the first term of attendance at these courses of graduate lectures will be indicated as "associate fellows," and those who complete a second term will be indicated as "fellows."

At the first convocation, more than five hundred physicians received certificates. Physicians may participate either in the extra-mural courses or in the intramural courses offered at the University of Michigan Medical School and Wayne University College of Medicine.

Dr. Henry A. Luce, F.A.C.P., Detroit, presided at the convocation, and Dr. James D. Bruce, F.A.C.P., Ann Arbor, Vice President in Charge of Graduate Education at the University of Michigan, delivered an address on "The Challenge of Medical Service."

Dr. Joseph C. Doane, F.A.C.P., Philadelphia, is Editor of "Modern Hospital." A special issue last September marked the twenty-first anniversary of its founding.

Dr. Philip I. Nash, F.A.C.P., Brooklyn, President-Elect of the Medical Society of Kings, and Dr. John P. Peters, Professor of Medicine at Yale University School of Medicine, New Haven, were the principal speakers at a symposium on "The Future of American Medicine," October 21, under the auspices of the Interne Council of America.

Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y., and Dr. Robert L. Levy, F.A.C.P., New York, N. Y., were among the guest speakers at the seventh Post Graduate Medical Assembly of South Texas held at Houston in November.

Dr. Andrew D. Hart (Associate) has been appointed Professor of Clinical Medicine and Director of Student Health at the University of Virginia, Charlottesville.

The Tenth International Congress of Military Medicine and Pharmacy will be held in Washington, D. C., May 7–15, 1939, under the Presidency of Major General Charles R. Reynolds, F.A.C.P., Surgeon-General of the U. S. Army. Invitations to participate have been sent to all parts of the world by the President of the United States, and many countries have already sent acceptances.

Under the leadership of Dr. Walter L. Treadway, F.A.C.P., Assistant Surgeon-General of the U. S. Public Health Service, a symposium on mental health will be presented before the Section on Medical Sciences of the American Association for the Advancement of Science, Richmond, Va., December 28–30.

The American Psychiatric Association, the U. S. Public Health Service, the Mental Hospital Survey Committee and the National Committee for Mental Hygiene are assisting. It is said that this is the first time in the history of American psychiatry that the subject of mental health has received special attention as a major topic on the program of this large scientific body, which has an active membership of over nineteen thousand, and an affiliate membership of three-quarters of a million.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, addressed the Tippecanoe County Medical Society at La Fayette, Ind., November 8, on "Newer Developments and Common Misconceptions of Allergy."

A meeting of the Maine members of the American College of Physicians was held at the Maine General Hospital in Portland on December 2. The scientific program follows:

1. Chronic Non-tuberculous Pulmonary Disease, with motion pictures—Dr. Francis J. Welch, Portland.
2. Observations in Coronary and Renal Injection Studies—Dr. Julius Gottlieb, Lewiston.
3. Laboratory Diagnosis of Typhoid Fever—Dr. Mortimer Warren, Portland.
4. Bachman Skin Tests and Eosinophil Counts in Individuals Who Have Previously Suffered from Trichinosis—Dr. Richard S. Hawkes, Portland.
5. Cardiac Infarction Involving the Lateral Wall of the Left Ventricle—Dr. E. H. Drake, Portland.

POST-CONVENTION TOUR TO MEXICO CITY

(Consult page 16 of the Advertising Section for detailed announcements concerning this Post-Convention Tour following the New Orleans Session of the College, March 27–31, 1939.)

Mexico City has been traditionally the center of national life since long before the Spaniards discovered the American Continent. It is today the center of the cultural, social, economic and political life of Mexico. Mexico City is to the Mexicans what Paris is to the French.

The Mexico City of today that you will see is entirely different from the original crude village that was its seed, and from the proud capital of the Aztecs that Cortez saw as he gazed down into the valley from the heights above. The original city was razed to the ground and a new one built in its place by Cortez, in the second, and greatest phase of his career, that of Colonizer. Many of those buildings, now several centuries old, you will see on your tour around the city.

In Mexico City centuries rub elbows. One's imagination is stimulated by its high lights and shadows. A modern assembly plant turns out tractors and six miles away the Indian is turning over the top soil with the help of a wooden plow, just as

his forebears did centuries ago. You admire the vast Palace of Fine Arts in all its modern marbled magnificence and within a stone's throw you will find a dozen buildings dating back to the 16th century. The fashionable "sub-deb" with a frock typifying "le dernier cri" may be walking down Madero Avenue and actually rubbing elbows with a group of "pilgrims" from some remote highland village, who have been frightened nearly out of their brown skins by the rush of the city's street traffic, where for twenty years not a horse drawn vehicle has turned. You see so many centuries in one day that it takes weeks to digest it.

The National Cathedral, begun in 1525 on the site of the principal pagan temple of the Aztecs and completed in 1575, recognized now as the oldest and finest religious structure in any of the Americas; the National Palace, built, by order of the King of Spain, to replace the burnt and pillaged palace of Montezuma, in 1692; the National Museum where the ancient monoliths, pagan idols, and sacrificial stones of a forgotten race have been preserved; the National Pawn Shop, conceived and founded a full year before the American Revolution by a charitable man to lend money to the poor at low interest rates; the National University, scattered about the city and built, by the royal order of Charles V of Spain, a full century before the founding of Harvard; the House of Tiles and Iturbide Palace, on the Avenida Madero, in the heart of the modern business section, two places of unusual interest; the Paseo de la Reforma, Mexico City's "Fashion Lane" and streets of magnificent homes, that leads to the entrance to Chapultepec Park, and Chapultepec Castle, former home of the Presidents of Mexico and former palace of the Emperor.

Venturing afield in our explorations of this ancient and interesting country we shall see the Pyramids of San Juan Teotihuacan. These black, brooding monuments, that have been unearthed in the last few years, are of an indeterminate age and origin, but have been guessed by archeologists to antedate the Pharaohs' Tombs in the Valley of the Nile. The biggest of the group, the Pyramid of the Sun, is larger at the base than any of the Egyptian Pyramids and almost as tall. Queer carvings and symbolic writings decorate the interior chambers and set the world to guessing at their meanings, at the minds that conceived them and the hands that fashioned them untold centuries ago. Engineers who have seen the structure have marveled at the mathematical exactness of their erection, and have scratched their heads in wonder over what manner of man could have transported the huge blocks and set them one upon another by no other agency than manpower. They are a glimpse into the closed book of the past, a definite proof that man had a knowledge of art and the exact sciences long before our own civilization came into being.

Cholula was, at the time of the Conquest, the religious center of the Aztec Empire. It was here that Cortez, in his righteous wrath against the heathen practices of the high priests, conquered the city and set about to fulfill his vow that he would erect a church for every day in the year. There are over three hundred of them, beautiful examples of the artistic nature that the Cholulans must have had, for it was they and their descendants who built them under the lash of their Spanish masters. The Cathedral is regarded as the most beautiful religous edifice south of the Rio Grande.

Puebla, the third largest city in the Republic, is often called the "City of Churches." It is also the home of the renowned Talavera pottery and tile industry, and many of its homes and buildings are roofed and floored with the colorful and decorative material.

Cuernavaca is an exceedingly picturesque town with a delightful air of antiquity. Cortez built a palace here in 1530 and we shall see the same magnificent panorama that delighted him. The Cathedral was built in 1529 and Mass was said there a hundred years before the landing of the Pilgrims. You will wander through the plaza, the market, and the dozens of shoe shops in one of which you will probably buy a pair of woven leather sandals for which Cuernavaca is famous. Of course,

you will see Diego Rivera's frescos in Cortez' Palace and wander through the Borda Gardens which witnessed many of Maximilian's and Carlotta's tragic days.

The Monastery at Acolman looks like a massive fortress, but its facade and cloisters are arresting. The bizarre frescos painted hundreds of years ago will captivate you, though the ravages of time and flood have been unkind to some of them.

The present Basilica at Guadalupe which dates from 1709 was built in honor of the Virgin of Guadalupe, patron saint of Mexico and Latin-America. Here we may see a "pilgrimage" from some nearby or remote village, offering tribute to the beloved Virgin. The legend of her apparition before the humble Indian, Juan Diego, has gripped the heart and imagination of the Mexican people. There she is perpetually enshrined.

Puebla is one of the oldest cities in Mexico and one which most perfectly retains its colonial atmosphere. Its strategic position as key to the capital made it the center of strife for years. Puebla is a gem with its well laid out streets, its overpowering churches whose multicolored domes glisten in the Mexican sunlight and its famed Talavera pottery and tiles, which industry was brought over by the conquerors.

Xochimilco, the Floating Gardens, is a unique and beautiful combination of lakes, canals and gardens. We ride the canals in flat bottom boats, plying our way among the flower laden islands that have been formed by nature from floating masses of twigs and branches covered with earth. It is a rare and lovely experience to ride these shaded, flower-lined waterways whose quiet is disturbed only by the birds. No matter which way you look you see flowers on island gardens, pleasant looking Indians balanced in canoes offering flowers for sale or with musicians singing and strumming guitars. No streets and no houses face the canals and you will be punting along a world of islands and canals with everybody happy and gay.

OBITUARY

DOCTOR KALLMAN MEYER DAVIDSON

With the death of Dr. Kallman Meyer Davidson, F.A.C.P., Boston, Mass., in his seventy-sixth year, on July 22, 1938, there passed from our midst a striking personality embodying qualities which give a place of honor to the family physician. Cultured, keeping zealously abreast with medical progress, endowed with a good stock of common sense and a fine sense of humor, he was the beloved advisor of three generations.

He had been in active medical practice for over half a century, and since 1891 in Boston. He brought to our community at that time a combination of the best in Russian-Jewish culture with the thorough training in medicine afforded in Germany in the last quarter of the nineteenth century, under the direct influence of men like Hermann, Virchow, Koch, Ehrlich, Naunyn and Minkowski. Thus prepared and with a naturally keen and inquisitive mind he was from the first a pioneer in raising the standards of medical practice especially among the immigrant part of our population. This was recognized not only by the people he served but also by the leaders of the profession, as shown by the friendship in those days of such men as Frederick C. Shattuck, Maurice H. Richardson and Reginald H. Fitz.

Particularly noteworthy was his active leadership in developing hospital service among his people here in Boston. In 1903 he was the prime mover in the organization of the Mount Sinai Dispensary, and in 1913 he was a leader in the founding of the Beth Israel Hospital, which has since developed into an outstanding institution.

Doctor Davidson was an indefatigable worker and always considered the practice of medicine as clinical research. He loved books and read extensively the medical literature. Ever young in spirit and in his interests he was a familiar figure at medical gatherings, and found great pleasure in his membership in the American College of Physicians.

He was a man of great fortitude and bore most courageously two calamities in his life—the loss of his beloved wife and more recently the untimely death of his brilliant son, Dr. Percy B. Davidson.

His memory will long be cherished.

HYMAN MORRISON, M.D.

DOCTOR ARTHUR EVERETT AUSTIN

Dr. Arthur Everett Austin, F.A.C.P., Boston, Mass., died at Windham, N. H., August 22, 1938; aged, 77 years.

Dr. Austin was born in 1861. After securing an A.B. degree from Bowdoin College in 1883, he went on to the Harvard University Medical School, where he received a degree of M.D. in 1887. In the same year he also received a degree of A.M. from Bowdoin College. In 1895 and 1897, he pursued postgraduate work in biochemistry at the University of Berlin, and in 1904–05 he took postgraduate work in gastro-enterology at the University of Vienna. Later he held the chair of Professor of Biochemistry at the University of Virginia and also at the University of Texas, and at his death was Professor Emeritus of Theory and Practice of Medicine at the Tufts College Medical School in Boston. He has served on the medical staffs of the Mt. Sinai Hospital and the Massachusetts General Hospital in Boston, and served as Major in the Medical Corps, U. S. Army, during the World War. His interest was primarily in diseases of the digestive tract, and he wrote various papers concerning such diseases. He was a member and former councillor of the Massachusetts Medical Society; member of the American Medical Association; and had been a Fellow of the American College of Physicians since 1920.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts.

DOCTOR JAMES ALLEN JACKSON

Dr. James Allen Jackson, F.A.C.P., died December 1, 1938, of leukemia. For the past eighteen years he was Superintendent of the Danville State Hospital for Mental Diseases. He was born in Upatoi, Ga., attended the University of Georgia and was graduated from Jefferson Medical College

of Philadelphia in 1906. He served as Resident Pathologist at the Philadelphia General Hospital, 1906 to 1908, and as Pathologist to the Central Indiana Hospital for the Insane from 1908 to 1910. He returned as Chief Resident Physician to the Philadelphia Hospital for Mental Diseases, where he served from 1910 to 1920. In addition to being Superintendent of the Danville State Hospital, he was Consultant to the George F. Geisinger Memorial Hospital, Bloomsburg Hospital and Williamsport Hospital; also Consultant-at-large in Mental Hygiene to the United States Public Health Service. He was a member of the Montour County Medical Society, Pennsylvania State Medical Society, Philadelphia Psychiatric Society, Philadelphia Neurological Society, American Medical Association, American Psychiatric Association, and had been a Fellow of the American College of Physicians since 1923.

Dr. Jackson wrote extensively on mental hygiene, and organized a chain of mental hygiene clinics in central Pennsylvania to serve those unable to be admitted to Danville. He was 33d degree Mason, and a member of the Editorial Staff of the Modern Hospital Magazine.

Dr. Jackson was a tireless worker. In addition to his professional skill and energy, he enjoyed the friendship and esteem of a large circle of friends. The profession and the community have, in his death, lost an outstanding leader.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DOCTOR JOSEPH MILLEN KING

Joseph Millen King (Fellow), Los Angeles, died October 27th on his 66th birthday. He was sitting in his automobile at the time about to leave his home for a professional call. Though he had had a coronary disease and knew the possibilities he kept working whenever he felt able.

Dr. King was born in the Parish of St. James, New Brunswick. He early moved to Pennsylvania, doing his pre-medical work at Geneva College. In 1889 he moved to San Diego. After teaching school for a couple of years he entered the College of Medicine of the University of Southern California, where he was graduated in 1895. Dr. King was a member of his County and State Associations and a Fellow of the A.M.A. He was a past President of the Los Angeles County Medical Association, the Southern California Medical Association and the California State Medical Association. He was a past President of the Los Angeles Clinical and Pathological Society of which he was also a founder member. He was a Clinical Professor of Medicine in the Medical School of the University of Southern California at the time of his death.

Dr. King did graduate work at Johns Hopkins in 1904 and at Berlin, Munich and Vienna in 1912–13. Throughout his professional life Dr. King was a member of the Staff of St. Vincent's Hospital, at one time being

Chairman of the Staff. He was also a member of the Staff of several other Los Angeles Hospitals. In all his professional circles his friendliness, forceful personality and sage counsel were highly valued. He was a fine man and a good physician whose memory will live long after him.

EGERTON CRISPIN, M.D., F.A.C.P.,
Regent.

DOCTOR DAVID R. CLARK

Dr. David R. Clark (Associate), of Detroit, Michigan, died July 3, 1938, after a year's illness.

Born January 26, 1874, in Port Clinton, Ohio, he was graduated from the University of Michigan Medical School in 1895. After several years' practice in Niles, Michigan, he came to Detroit where he specialized in psychiatry.

For over forty years, Dr. Clark had been Senior Medical Officer of St. Joseph's Retreat, Dearborn, and for twenty years of the psychopathic department of Detroit Receiving Hospital. He was past president of the Detroit Society of Psychiatry, and a member of the American Psychiatric Association. At the time of his death, he was one of the elder of the Detroit group of psychiatrists.

Besides his institutional appointments, Dr. Clark had a large practice of devoted patients. An able psychiatrist, he was also an earnest student of sociology. He was active in advocating hospital additions and improvements in the care of mental cases in this state.

Greatly beloved by the profession for his keen clinical insight, warm friendship to his friends and loyalty to his ideals, Dr. Clark will be greatly missed by the physicians and the public whom he so ably served.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan.

DOCTOR FELIX P. CHILLINGWORTH

Doctor Felix P. Chillingworth (Fellow), aged 55 years, died at his summer home in Concord, Massachusetts, on June 29, 1938, after a serious illness of eight months.

Doctor Chillingworth was a graduate of the Yale School of Medicine in 1907, and practiced medicine in Hoddam, Connecticut, for four years, but his aptitude for research and teaching found an outlet when he went into the Department of Physiology at Kansas University in 1912, and then in 1913 to Tulane University in New Orleans where until 1919 he was Assistant Professor of Physiology. During the years of the war, in addition to his medical teaching, he was physician to the Louisiana Leper Colony at Carville which later was taken over by the United States Government. In 1919 he became Professor of Physiology in the Tufts Medical and Dental Schools

in Boston, Massachusetts, and in 1929 Professor of Pharmacology in the same schools.

His research publications have been extensive both in British and American medical journals.

Doctor Chillingworth was a great lover of travel and in his later years took up etching as a hobby. He was a member of various social clubs in Massachusetts, Connecticut and Louisiana, and held membership in many medical and scientific organizations.

He is survived by his widow, Gertrude Smith Chillingworth, two sons, William Felix Chillingworth and Philip Oliver Chillingworth and a sister, Lillie M. Bryant.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts.

DOCTOR LOUIS M. WARFIELD

Dr. Louis M. Warfield, of Milwaukee, Wisconsin, died September 28, 1938. Dr. Warfield was born in Savannah, Georgia, in 1876; received his A.B. degree in 1897, and M.D. degree in 1901 from Johns Hopkins University. Immediately after graduating, he went to the Rockefeller Institute, where he did work in pathology. Following this, he studied abroad for a year and one half, after which he returned to Savannah, and entered practice. He then went to St. Louis, where he was Secretary of the Anti-Tuberculosis Association, and from St. Louis, he came to Milwaukee, and was in charge of the medical service at the Milwaukee County Dispensary and Hospital. During the war, he held a commission as Major, and was stationed at Jefferson Barracks, Missouri, where he was chief of the medical service. For two and one half years (1922–1924), he was Professor of Medicine at the University of Michigan. Following his resignation, he spent several months abroad, and again returned to practice medicine in Milwaukee with his special interest centered in cardiovascular diseases. In 1925, Dr. Warfield established the Milwaukee Internists Club, which is now the Milwaukee Society of Internal Medicine. He was a member of the American Medical Association; the American Association of Physicians; the American College of Physicians; was a past president of the Milwaukee Academy of Medicine; an emeritus member of the Central Society for Clinical Research; a member of the Chicago Internists Society; a past editor of the *Wisconsin Medical Journal;* and at his death president of the Wisconsin Anti-Tuberculosis Association.

ROCK SLEYSTER, M.D., F.A.C.P.,
Governor for Wisconsin.

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